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# CHRONIC TUBERCULOUS MEDIASTINITIS AND MEDIASTINAL LYMPHADENITIS<sup>1</sup>

*Report of Two Cases Illustrating Certain Complications with Surgical Measures  
for Their Relief*

ARTHUR H. AUFSES AND HAROLD NEUHOF

As a background for the 2 cases to be described and discussed in this paper, a brief analysis of the pertinent literature will be set forth. It will be noted that some of the cases are proved to be tuberculous, whereas in others the diagnosis of tuberculosis is an assumption. The diagnosis in many of the cases in the literature was only established at postmortem examination.

The literature reviewed, as portrayed in the bibliography, included, in the main, only those publications which were germane to the 2 cases reported here, namely, chronic fibrosing tuberculous mediastinitis causing pressure symptoms in the superior mediastinum and tuberculous mediastinal lymphadenitis causing esophago-tracheo-bronchial fistulae. There is a voluminous literature on other allied disease processes, such as tuberculous mediastino-pericarditis, constrictive pericarditis and bronchial perforation of tuberculous mediastinal lymph nodes (both caseous and calcified). These were neither reviewed nor included in the bibliography.

The term mediastinitis should be restricted to inflammatory processes in the mediastinal tissue spaces. When such an infection occurs by extension from adjacent areas such as the pleura or the cervical region there may be a true mediastinitis in the above sense. In addition, the mediastinitis which occurs following esophageal perforation may be considered as a distinct entity.

Mediastinal lymphadenitis may remain confined to the nodes or may rupture into the esophagus, a bronchus or both without causing any mediastinitis. On the other hand, there may be concomitant inflammation of both nodes and mediastinal tissues. The clinical differentiation between mediastinal lymphadenitis and mediastinitis or a combination of the two is obviously extremely difficult. Even at the time of operation or postmortem examination an accurate classification may be impossible.

The bizarre clinical manifestations which may appear often make it difficult to render a correct diagnosis, as will be seen in the following survey. Our purpose in presenting 2 cases in which the diagnosis has been established during life is to portray the clinical features of these extraordinary lesions, one form of which is not generally recognized clinically, namely, a benign chronic form of the disease.

Although tuberculosis of the mediastinal lymph nodes is usually found in children, its occurrence in the adult is not uncommon. As a disease of adult life, without radiological evidence of pulmonary tuberculosis, the diagnosis is difficult to make. In children as well as in adults, the disease may assume one of two courses: (1) generalized dissemination of tuberculosis with early death; (2) a

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chronic form in which the disease remains localized largely in the mediastinal nodes.

When the disease remains confined essentially to the mediastinal nodes, it may progress to eventual cure with calcification or it may lead to complications because of pressure upon, or ulceration into, the neighboring viscera. A diffuse lymphangitic tuberculous mediastinitis may also occur. The fibrosis which may result from the healing of such a process can produce symptoms by involvement of the mediastinal organs.

During the period of caseation, the perforation of a tuberculous mediastinal node into a bronchus will frequently lead to a tuberculous pneumonitis. After calcification has occurred, a bronchial stenosis may be caused by extrinsic pressure, or the node may perforate into the bronchial lumen from which it may be expectorated or removed bronchoscopically. Such a condition is commonly referred to as broncholithiasis, and may result in pulmonary atelectasis and suppuration. If perforation occurs into a large blood vessel, hematogenous tuberculosis will ensue.

Enlarged tuberculous tracheobronchial nodes may cause pressure symptoms. Two cases which were operated upon successfully have been reported. In one case, from the Massachusetts General Hospital, a mass of nodes causing dysphagia was removed, with uneventful recovery. The second case, a patient with tuberculosis of the lungs and pleura, reported by Walz in 1912, had ten large anterior mediastinal masses, weighing 605 g., removed because of severe dyspnea and cyanosis.

Primary tuberculosis of the esophageal mucous membrane is so rare a condition that most pathologists doubt the authenticity of the few recorded cases. Tuberculous ulcerations of the esophagus are the result of perforation of a caseating mediastinal node through the esophageal wall. When this node also perforates into a bronchus, a fistula between the two organs is produced. Most of the pathological specimens demonstrating this condition reveal a fistulous opening into each organ, with a caseating abscess cavity situated between them.

The nodes causing the esophageal fistula may also perforate directly into the pleural cavity, producing an empyema; this has been reported by Martens, Sayago, Flexner, Kanter, Valli, and Blauvelt. They may also ulcerate directly into the lung across the mediastinal pleura, producing a pulmonary abscess (Westergren, Kopstein).

In children, aside from the congenital type of esophago-tracheal fistula, all non-traumatic fistulae between the esophagus and the tracheobronchial tree are due to tuberculosis (Zuppinger). These are usually fatal shortly after their appearance and, therefore, are rarely diagnosed clinically.

In adults, the great majority of fistulae between the esophagus and the tracheobronchial tree are due to carcinoma. Sirot, in 1898, collected 107 cases of such fistulae, most of which were due to carcinoma (only 17 to tuberculous lymphadenopathy). Moersch and Tinney reported 39 cases from the Mayo Clinic, 4 of which were on a tuberculous basis. Monserrat, in a review of the literature up to 1940, collected 681 cases of which 14 were tuberculous. He added 3 cases in

children discovered at postmortem examination. In 1941, Arnstein reported the postmortem study of 135 cases of tuberculosis of the mediastinal and bronchial lymph nodes in elderly people. Some of these had associated pneumoconiosis. He found 34 esophageal diverticulae, 13 of which had perforated into the bronchial tree.

In adults, the usual course of events is the formation of an esophageal traction diverticulum at the site of the "tracheal bifurcation lymph node." The esophageal perforation occurs at the tip of this diverticulum. Hawes has demonstrated the various changes in the esophagus resulting from tuberculous mediastinitis. Traction diverticulae are the most common lesions, due to fibrosis in the peri-esophageal tissues. The bronchial opening is situated in one of the main bronchi. Multiple openings into both bronchial trees have been reported by Westergren and Heine.

Tuberculous abscesses of the posterior mediastinum may also be associated with caries of the vertebral bodies. These abscesses may burrow into the lung and may communicate with the esophageal lumen through a fistula at the site of a diverticulum (Brand).

When the esophageal fistula communicates directly with the pleural cavity, an empyema ensues. After either spontaneous or surgical drainage, these patients may live for a long period of time. The patient reported by Martens had remained in good health for seven years from the time of the appearance of the fistula. Osler and Downes reported cases of esophago-pleural fistulae which opened spontaneously on the right anterior chest wall, having burrowed outside of the lung across the pleural space. Osler's patient lived for twenty years; the patient of Downes gained 40 pounds in one year after gastrostomy.

When the fistula enters a bronchus, pulmonary infection usually occurs and the prognosis is poor. If the fistula is small, the patient may maintain his nutrition by avoiding fluids. Furthermore, he may find that, by lying in a certain position during deglutition, ingested foods will not enter the fistulous opening. Pape reported a case in which a fistula was present for two years with gradual improvement in the patient's general condition and diminution in the amount of bronchial spilling. The presence of many calcifications in the lungs, mediastinal adhesions and a lower lobe primary complex pointed to a tuberculous lymphadenopathy as the etiological factor.

Gagelmann reported the postmortem findings of 3 cases of esophago-bronchial fistulae due to calcified lymph nodes. Clinical symptoms suggestive of a fistula were mild in character and had been present for only a short period before death. In case 1, presented here, the fistula closed approximately four months after its appearance. A review of the literature has not revealed any other spontaneous closure of a proved tuberculous esophago-bronchial communication.

When tuberculosis affects the mediastinum as a diffuse lymphangitic process, it may eventually progress to a chronic stage. This may cause symptoms due to involvement of the mediastinal structures by the dense fibrosis which ensues. When this occurs in the posterior mediastinum, esophageal deformities and diverticulae may develop. In the anterior mediastinum, obstruction of the super-



rior vena cava and innominate veins is the most common pathological process. Paralysis of the recurrent laryngeal, phrenic, cervical sympathetic and vagus nerves has also been reported.

Duchek, in 1854, reported a number of cases of obstruction of the superior vena cava, one of which was due to tuberculous mediastinitis. Later reports of isolated cases were made by Chvostek, Le Tohic, Balzer, Martelli, Duckworth, and Samek. Boonacker reported a case of caval obstruction due to tuberculous mediastinitis, with marked laryngeal edema as a complication. In 1904, Fischer collected 220 cases of superior caval obstruction and found that 1.5 per cent were due to tuberculous phlebitis and 6 per cent to traction and compression by scar tissue. Radonicie, in 1910, in a discussion on tuberculous fibrosing mediastinitis, stated that he had seen 27 cases, but gave no details.

In 1913, Sorel reported a case of superior vena cava obstruction with hemorrhagic pleurisy and hemiplegia due to tuberculosis. Howard, two years later, reported 2 cases, one of which was on a tuberculous basis.

Milles, in 1932, reported a patient who died two days after exploratory thoracotomy. Death was thought to be due to interference with the collateral circulation because of ligation of the internal mammary vein. The postmortem findings were as follows: "A cartilaginous, rather poorly-defined mediastinal mass was found adherent to the lung and encircling the superior vena cava, about 4 cm. above the right auricle. The lumen was 2 mm. in diameter, the wall was thickened to 7 mm. by dense cartilaginous connective tissue, and the center of the encircling mass was made up of cheesy, necrotic material of the shape and appearance of a broken-down lymph gland. Although no tubercle bacilli were found, the microscopic picture led to the diagnosis of chronic fibrocaceous tuberculosis of a mediastinal lymph gland."

Ehrlich, Ballon and Graham, in 1933, found references in the literature to 309 cases of superior caval obstruction, including Fischer's cases reported previously. In 1934, Kornblum and Osmond described a case of adhesive pericarditis, with symptoms of caval obstruction. At postmortem examination, the lumen of the superior vena cava where it entered the pericardium was almost completely obliterated by an adhesive process which was found to be tuberculous on microscopic examination. Ochsner and Dixon, in 1936, separated the cases of superior vena cava thrombosis from the general group of obstructive lesions. They collected 120 cases and found that 4 (3.3 per cent) were due to a tuberculous phlebitis, and 10 (8.3 per cent) were due to tuberculous mediastinitis.

Szour and Berman, in 1936, reported a case in which the main symptom was edema of the right arm. At postmortem examination, pulmonary and laryngeal tuberculosis was found with paratracheal and parabronchial adenitis. There was an adhesive periphlebitis around the superior vena cava, with thrombosis of that vessel extending into the right subclavian vein. Gray and Skinner (1941) reported 3 cases of occlusion of the superior vena cava treated surgically by removal of bands of constricting tissue. Improvement was noted in 2, and the third patient died. Specimens from all 3 removed at the time of operation were

reported as fibrous inflammatory tissue. A postmortem examination of the fatal case showed calcified lymph nodes; the lesion, therefore, was considered to be tuberculous.

There are a number of reported cases of chronic fibrosing inflammatory processes constricting the superior vena cava, but because of the inability to demonstrate a definite pathological picture, compatible with tuberculosis, they cannot be classified as tuberculous mediastinitis. Wilkins, in 1883, and Meigs, in 1885, reported cases of superior caval obstruction due to fibrosing lesions. Wilkins' case was probably on a traumatic basis and Meigs' was of an inflammatory character. Freedlander, in 1945, reported a case in which a dense infiltrating mass was found around the cava. Specimen showed only hyperplasia of lymphoid tissue and chronic inflammation of fibrous connective tissue. Guinea pig inoculation was negative. Cleland, Blasingame, and Buzzard have also cited similar pathological findings.

Erganian and Wade reported 3 cases of fibrous chronic mediastinitis with superior vena cava obstruction. No specific etiology could be established. In 2 cases the tissue consisted of dense, eosinophilic, collagenous fibrous tissue. It is possible that some of these cases were due to tuberculosis which was not diagnosable on the biopsy specimen. Even in those that came to postmortem examination, the fibrosis had progressed to such a degree that the specificity of the original inflammatory process was no longer recognizable. In other cases, syphilis has been considered to be the causative factor because of a positive serology or other stigmata of the disease (Knox).

Nerve paralyses due to tuberculous mediastinitis have been reported by Arnstein, Koester, Rousseau, and Portmann. Arnstein, in 135 cases, found the left recurrent laryngeal nerve involved 47 times, the right nerve twice and both nerves 4 times. Branches of the vagus were involved in 7 cases, the right phrenic in 4 and the left phrenic in 6. He did not state whether there was any clinical evidence of these pathological findings. Koester reported a left phrenic nerve paralysis. Rousseau observed a left Horner's syndrome and left recurrent nerve paralysis in the same patient. Portmann cited 16 cases, as reported by Avellis, in which the left recurrent nerve was involved 14 times and the right recurrent twice.

Case 2 reported here is, as far as can be determined, the first one in which the diagnosis was established from a biopsy taken at the time of operation. It is difficult to decide whether the improvement which followed operation was due to a decompressive effect, or to an increase in the collateral circulation. In any event, the chest was closed with no attempt to effect a thoracic decompression. Interestingly, Aguilar has recently advocated the use of a decompressive mediastinotomy for superior caval obstruction due to tuberculous mediastinitis. He advocates the resection of three or four costal cartilages on one or both sides. On the other hand, the improvement may be similar to that seen after an exploratory laparotomy for tuberculous peritonitis.

## CASE REPORTS

*M. M.* (#538230), a female, 37 years old, was admitted to The Mount Sinai Hospital on September 11, 1944, with the chief complaints of cough and expectoration of foul smelling sputum.

Since April, 1944, she had had a cough with expectoration of one to two cupful of whitish sputum, which was occasionally blood-tinged. X-ray examination in May, 1944 (figure 1) had shown a shadow in the left chest, close to the mediastinum. This had developed with no previous symptoms or possible etiological factor. She had had some sticking chest pain to the left of the sternum and in the left scapular region. Three weeks before admission there had been a moderate hemoptysis. Five days before admission, the sputum had suddenly become foul and she had five shaking chills, with temperature ranging between 102° and 106°F. There had been a loss of 30 pounds since the onset of her symptoms.

There was nothing relevant to the present illness in her past history, nor was there a history of tuberculosis in the family.

The patient was an acutely ill female with a severe cough and considerable foul expectoration. There were dulness and diminished breath sounds in the left infraclavicular region. There was no clubbing of the fingers. Temperature on admission was 104°F.; hemoglobin 68 per cent; white blood cells 18,000. Wassermann and blood culture were negative. Sputum culture showed a variety of organisms. Electrocardiogram was normal. X-ray examination of the chest (figure 2) showed a large abscess cavity, two inches in diameter, situated in the anterior part of the left upper lobe, containing a small quantity of fluid. The abscess cavity extended mesially to the left sternal border and its centre was in line with the costochondral junctions. The upper border reached the upper border of the first rib and the lower border extended to the second intercostal space anteriorly. There was a moderate amount of pulmonary infiltration about the abscess, and there were faint small mottled infiltrations in the antero-axillary portion of the left upper lobe. The long fissure was sharply outlined.

A diagnosis of putrid lung abscess of the left upper lobe, of unknown etiology, was made, and thoracotomy and drainage of the abscess was performed on September 13, 1944. A segment of the second rib anteriorly was removed. The lung was found to be adherent beneath this area. Aspiration yielded foul pus, and the abscess was opened, its overlying shell of lung removed, and the cavity packed. The presence of a bronchial fistula was established. Pathological examination of the pieces of the cavity wall removed at operation showed: "Subacute pleuritis (fibrous tissue proliferation including fibrin) and pneumonia with incipient organization. A second fragment of tissue shows necrotizing pneumonia in the depths."

The clinical course following operation was not that which is usually seen after drainage of a localized putrid lung abscess. The drainage from the cavity remained foul smelling, and the cough, sputum and low grade fever persisted. On September 24, 1944, X-ray

FIG. 1. (Upper left) Case 1. May, 1944. Four months prior to the development of the putrid lung abscess.

FIG. 2. (Upper right) Case 1. September 12, 1944. Putrid lung abscess, left upper lobe.

FIG. 3. (Centre left) Case 1. September, 1945. Lung abscess healed, slight mediastinal widening.

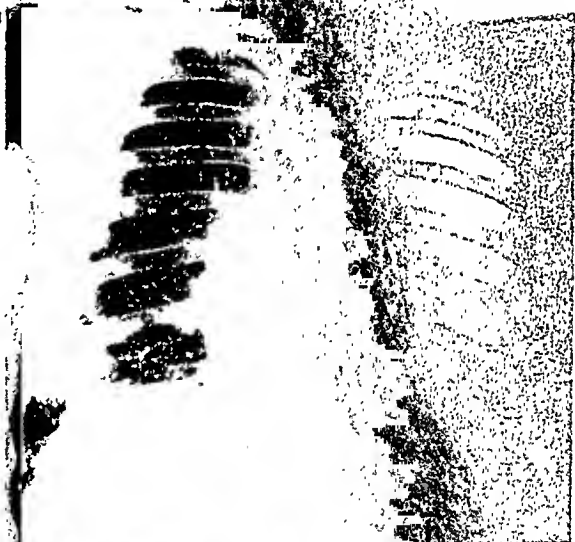
FIG. 4. (Centre right) Case 1. March, 1946. Increase in mediastinal widening.

FIG. 5. (Lower left) Case 1. May, 1946. Right pyopneumothorax.

FIG. 6. (Lower right) Case 1. June 5, 1946. Esophageal diverticulæ and esophago-bronchial. (The latter is not visible in the reproduction.)



2



6

FIGS. 1-6

examination revealed a persisting homogeneous shadow medial to the drained area. This shadow extended directly backward into the medial portion of the left chest from the level of the first to the third ribs anteriorly. This was thought to represent an undrained focus and, accordingly, revision of the wound was performed on September 27, 1944. This procedure consisted of aspiration through the medial wall of the previously drained abscess. Thick, grumous non-fetid pus was obtained, and an incision was made into this area. No definite abscess cavity was found in this region which was filled with inspissated pus and debris. It was felt that this lesion was either very close to or possibly within the mediastinum. The operative area was packed with radiopaque gauze. X-ray examination performed immediately after operation showed that the density previously seen had been drained.

Following this operation, the patient did well. The cough and sputum subsided, drainage from the cavity lessened and lost its odor, and the general condition of the patient improved. X-ray examination showed a marked resolution of the pneumonic process around the abscess but the homogeneous density medial to the original abscess still persisted. She was discharged on October 26, 1944, with a drainage tube *in situ*. She was seen at regular intervals in the follow-up clinic. Two months later, X-ray examinations showed a persistence of the shadow in the medial part of the left upper lobe; there now was a widening of the superior mediastinum. The drainage tract closed completely during this period.

In January, 1945, the patient complained of wheezing noises in the chest on expiration, and these were found on physical examination. She was readmitted for bronchoscopy on January 29, 1945. She had regained her original weight, and clubbing of the fingers was now present. Bronchoscopy revealed the following: The left upper lobe bronchus was patent and there was a small quantity of jelly-like mucoid secretion present. In the right lung, at the beginning of the lower lobe bronchus at the level of the mesial branch, there was a smooth, white, glistening sessile mass about 4 mm. in diameter on the anterior wall; alongside was a smaller, red, firm mass about 3 mm. in size; they obstructed about three-fourths of the lumen. Both masses were removed. Pathological examination revealed that the larger specimen was tuberculous granulation tissue covered by squamous epithelium, and containing tubercle bacilli.

Another bronchoscopic examination two weeks later showed a similar mass in the right lower lobe bronchus. After its removal, an ulcer could be seen on the medial anterior wall, involving mucosa and cartilage. The picture was one usually seen with a perforating peribronchial lymph node. This specimen also showed tubercle bacilli on examination. Upon further questioning, the patient now stated that she had received eight X-ray treatments to her chest in May, 1944, for "swollen glands."

Sectional roentgenograms showed a displacement of the lower trachea to the right. There was also a downward displacement of the left main bronchus which appeared somewhat narrowed as a result of pressure by enlarged tracheobronchial lymph nodes. The sections also showed lobulated shadows in the region of the right hilum, which suggested the presence of large lymph nodes. None of the right bronchi appeared to be narrowed. The patient was entirely afebrile during this admission, and she was discharged on February 24, 1945.

For the following six months she went to the country where she was on a rest regimen. During this time she was relatively well except for two episodes of chills and fever, one in June, the other in July. Both of these responded promptly to penicillin therapy. She was readmitted on August 16, 1945. For two weeks before admission she had had chills and fever which, this time, did not respond to penicillin. Physical examination showed nothing different from that which had been observed previously. The scar at the site of

drainage of the lung abscess was firmly healed. She complained of slight cough and expectoration.

During the first seven days in the hospital she had daily chills, with temperature rises of 105° to 106°F. On the fifth day penicillin therapy was begun in dosage of 20,000 units every three hours. On the eighth day the chills ceased, and the temperature returned to normal a few days later. Nevertheless, penicillin was continued for one month. Two blood cultures during the first week of hospitalization were negative. Many sputum examinations were negative for tubercle bacilli. These included cultures and guinea pig inoculations. An enlargement of the liver and spleen was noted. Congo red test showed 25 per cent retention, and bromsulphalein test showed less than 5 per cent retention after thirty-two minutes.

Bronchoscopy on August 28, 1945 showed a thickened spur between the right upper and right main bronchus. There was some scarring of the branches of the right upper lobe bronchus. There was marked thickening of the spur of the left upper lobe bronchus, with edema causing crescentic narrowing. On the posterior surface of the left main bronchus, there was a minute area of granulation tissue, 2 mm. in diameter. Another bronchoscopy on September 13 showed small granulomatous lesions on the posterior wall of the right upper lobe bronchus. X-ray examination on this admission showed no change from the previous films (figure 3). The widening of the superior mediastinum was still present. There was no roentgenological evidence of osteomyelitis of the sternum.

The chills and fever were thought to be due to an exacerbation of the mediastinal tuberculous lymphadenopathy, with possible hematogenous spread causing the hepatosplenomegaly. On the other hand, the response to penicillin therapy of all three febrile episodes appeared to negate this viewpoint. The patient was discharged to return to the country for continuance of rest therapy.

The patient was next seen at Montefiore Hospital, on May 14, 1946, where she had been sent for radiotherapy. In the interim, she had entered the Mayo Clinic in January, 1946, where X-ray examination had shown a widened superior mediastinum, more prominent on the right. They reported that eleven sputum examinations, as well as a guinea pig inoculation, had been negative. Bronchoscopy at that time had revealed a polypoid tumor mass on the lateral wall of the right lower lobe bronchus. The entire mass was removed and this was reported as tuberculous tissue. An X-ray in March, 1946 had shown a marked widening of the superior mediastinum (figure 4).

While waiting to be admitted to Montefiore Hospital, she had developed pain in the right chest, increased cough and expectoration, and high fever. X-ray examination on admission (figure 5) revealed a hydropneumothorax on the right side. Aspiration yielded 1,500 cc. of foul smelling pus. Aspiration and instillation of penicillin were performed daily. Parenteral penicillin was administered as well.

It was noticed that the patient had severe paroxysms of coughing during swallowing of fluids. She stated that this symptom had been present for three weeks before admission. Solid foods did not cause so much difficulty.

Ten days after admission the scar on the left anterior chest became reddened, and there was a considerable amount of subcutaneous emphysema over the left chest and neck. The wound opened, discharged a moderate amount of purulent material and remained open as a bronchocutaneous fistula.

With penicillin therapy, the foulness of the pleural fluid disappeared, and the patient's general condition improved. On June 5, a barium swallow (figure 6) revealed an esophago-bronchial fistula. This was situated at the tip of a traction diverticulum at the level of the tracheal bifurcation.

On June 10, the empyema cavity was drained. Under local anesthesia, segments of the

seventh and eighth ribs were removed posteriorly. A large empyema cavity was found containing pus and fibrin. A bronchopleural fistula was present in the apex of the lower lobe. Because of a large anterior loculation, counterdrainage was performed in front.

During this period there had been gradual increasing edema of the legs. Congo red test showed 58 per cent retention and blood proteins were: total, 6.5 g. per 100 cc.; albumin, 3.2 g.; globulin, 3.4 g.; on July 10, they had dropped to 5.0 g., 2.2 g. and 2.18 g., respectively. It was felt that the hypoproteinemia was due to a combination of loss of fluid through the empyema cavity and inability to swallow a normal amount of food. Efforts were made to combat the deficiency with intravenous amino acids and as high a protein intake as was possible for the patient to ingest.

After the empyema cavity had been drained, methylene blue was given by mouth on a number of occasions. Although the patient coughed violently during swallowing, the dye never appeared in the empyema cavity. It was thought that the esophago-bronchial fistula had led to the development of a lung abscess which in turn had perforated into the pleural cavity, and that the intrapulmonary tract was probably too circuitous to permit the dye to reach the pleuro-pulmonary opening.

In order to place the esophago-bronchial fistula at rest and also to combat the hypoproteinemia, a gastrostomy was proposed. The patient refused operation on the grounds that her difficulty in swallowing was becoming less. Her observation was correct and soon she was able to take all her food with practically no cough. On a special diet of 3,800 calories and 196 g. of protein daily, the edema gradually disappeared.

An esophogram on September 4, 1946 revealed the traction diverticulae which were present previously, but there was no longer any evidence of an esophago-bronchial fistula. Furthermore, there were no longer any clinical symptoms to suggest its presence. On October 7, 1946, there was a sudden rise in temperature to 103°F., associated with increased cough. X-ray examination revealed a new infiltration in the right lower lobe. The empyema cavity had gradually reduced in size and was covered by healthy granulation tissue. The bronchopleural fistula was still present. Shortly after this febrile episode, the sputum became positive for tubercle bacilli for the first time.

In November, 1946, X-ray examination revealed diffuse infiltrations throughout the left lung. These appeared to be due to a tuberculous spread. Streptomycin therapy was begun on November 24, 1946. Bronchoscopy on January 8, 1947 showed the following: "There is a slight narrowing of the left main bronchus just below the left upper lobe orifice. There is a scar (dimple) in the right lower lobe bronchus on the mesial wall just below the middle lobe orifice. This may represent a healed perforation into the mediastinum." X-ray examination on January 9, 1947, six weeks after the onset of streptomycin therapy, revealed considerable clearing of the infiltrations in the left lung.

The patient's general condition continued to improve. The bronchocutaneous fistula at the site of the original lung abscess in the left upper lobe closed. The empyema cavity had been reduced to a small sinus with a bronchopleural fistula which could be heard only intermittently. She continued to gain weight, and when last seen in July, 1947, there was marked clearing of the pulmonary infiltrations (figure 7).

*E. M.* (#542879), a female, 35 years old, was first admitted to The Mount Sinai Hospital on May 11, 1944, with the chief complaint of swelling of the face, neck and arms.

Nine months before admission, a nonproductive cough appeared together with intermittent pain over the thoracic spine radiating to the anterior chest and left arm. The latter was worse at night. For four months there has been a bursting feeling in the head, and fulness in the throat. This has increased when the patient raised her arms.

For three months there has been progressive swelling of the head, neck and arms. During the last three weeks before admission, the patient noticed a narrowing of her left palpebral fissure and a decrease in the size of her left pupil. The left hand and arm became more swollen in the last week before admission and there developed slight shortness of breath on bending or walking. There has been no loss of weight.

The patient had had two attacks of dry pleurisy, one in 1929, the other in 1931. During March, 1943 the patient had been in another hospital where X-ray examination showed "a pneumonitis in the right mid-lung field and enlarged right hilar lymph nodes."

The patient was a markedly obese female, with puffiness of the face and neck. The rounded moon-face with loss of lines of expression, engorgement of large and small veins, and chemosis of the conjunctivae were pathognomonic of superior caval obstruction. Both arms were greatly swollen and there was evidence of increased collateral circulation



FIG. 7. Case 1. July 2, 1947. Clearing of pulmonary infiltrations. Thickened pleura at right base.

over the anterior left chest and arm. The anterior mediastinum was widened to percussion. There was a Horner's syndrome on the left. Venous pressures were 22 cm. of water in the left arm and 16 cm. in the right. Basal metabolic rate was -11 per cent. Blood pressures were: right arm, 100/72; left arm, 80/60; right and left leg 120/80. Tuberculin (1:100) test was positive. Blood examination and other laboratory tests were essentially normal.

X-ray examination on May 13, 1944 showed "a widening of the superior mediastinum by a mass which is situated anteriorly and extends further to the right than to the left. Its borders are ill defined. There is a linear shadow alongside the long fissure on the right which is due to exudate in the pleura. The right leaf of the diaphragm is somewhat elevated." (Figure 8.) Comparison with the film taken in January, 1944 showed little change.

On May 19, 1944, a mediastinogram was made after injection of air into the anterior mediastinum. This outlined "an indefinite mass which is mainly anterior but also is



present in the posterior mediastinum. It is separate from what appears to be thymus. There is a hilar adenopathy." On the same date, a venogram made after injection of dio-

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FIG. 8. (Top) Case 2. May 13, 1944. Widening of superior mediastinum.

FIG. 9. (Lower left) Case 2. June 20, 1944. Venogram showing obstruction in left subclavian vein.

FIG. 10. (Lower right) Case 2. November, 1944. Venogram showing obstruction and collateralization to diaphragmatic veins.

drast into the antecubital veins showed obstruction to the flow of the radiopaque material one inch to the right of the superior vena cava on the right side. On the left side there was no filling of the subclavian vein, due to obstruction in the region of the left axilla.

Collateralization into the left suprascapular veins was seen. Sectional radiography corroborated the presence of a mass in the upper anterior mediastinum. An enlarged axillary node which was removed showed no distinctive pathological picture. Bronchoscopy on May 29, 1944 was negative except for a "pushing in" of the posterior wall of the right main bronchus.

The preoperative diagnosis was obstruction of the superior vena cava by a mediastinal neoplasm. Because of a left Horner's syndrome, which could only occur by extension of the growth into the posterior mediastinum, it was felt that the tumor was infiltrating in character. Nevertheless, it was decided to perform an exploratory thoracotomy because of the possibility of encountering a remedial lesion.

On June 2, 1944, under cyclopropane intratracheal anesthesia, the thorax was opened through the third left intercostal space. The thymus or a soft mass in the thymic region was found to be pushed forward and arched over a firm mass which was diffusely infiltrating, without areas of softening. The mass, which was not demarcated, extended from the anterior limits of the mediastinum downwards over the arch of the aorta, backwards into the posterior mediastinum, and upwards toward the root of the neck. It extended indeterminately beyond the area that could be seen and palpated. A liberal specimen was removed, and the thorax was closed. The pathological report of the biopsy specimen was: "Hyalinized inflamed connective tissue including a caseous focus. Histology compatible with chronic fibrosing tuberculous mediastinitis."

Aside from a pleural effusion which was soon absorbed, the postoperative course was uneventful. Two weeks after the operation, it was apparent that the Horner's syndrome had disappeared. There was a recession in the subjective symptoms, and the facial swelling was definitely decreased. Venous pressures were: right arm, 16 cm. of water; left arm, 16.5 cm.

On June 20, after the injection of diodrast into the left antecubital vein, a venogram showed the radiopaque material to extend through the axillary and subclavian veins to the midline. (It did not enter the subclavian vein preoperatively.) The superior vena cava was not outlined. There was marked collateralization, and some filling defects were seen in the axillary vein, probably due to partial thromboses (figure 9).

The patient was discharged on June 23 and during the next five months had considerable relief. She was readmitted on November 27, 1944, because of a recurrence of pain in her left arm and dyspnea, and also for a check-up examination. Physical examination revealed swelling of the head, neck and arms, which was not so marked as before operation. There was slight ptosis of the left eyelid and the left pupil was smaller than the right. Venous pressures were: right arm, 19 cm. of water; left arm, 22 cm. Blood pressures were: right, 90/60; left arm, 100/70. Saccharin circulation time in the left arm was seven and one-half seconds.

A venogram, after injection through the left arm (figure 10), showed a small axillary vein, with obstruction at the superior mediastinum. The innominate vein could not be visualized. The hemiazygos vein on the left was seen, with an anastomosis at the level of the fifth thoracic vertebra across to the right side, outlining the right azygos. The diaphragmatic veins on the right were also filled. There was marked supraclavicular collateralization on the left. Venogram, after the injection through the right antecubital vein, showed none of the radiopaque material to enter the superior vena cava. Some collateralization was present and obstruction presumably occurred at the entrance of the innominate vein into the superior vena cava.

An esophogram revealed no definite abnormality except for slight posterior displacement at the level of the tracheal bifurcation.

The patient was seen again in December, 1945, at which time she stated that she had a marked increase in her symptoms during menstruation, but in between these periods she was relatively comfortable. Venous pressures were: 20.5 cm. of water in the left arm and 17 cm. in the right. Circulation times were twenty-four seconds and fifteen seconds in the left and right arms, respectively. Although there was a slight ptosis of the left eyelid, the pupils were of equal size, and a sweating test showed no evidence of a Horner's syndrome.

When last seen in February, 1947, the findings on physical examination were similar to those of December, 1945. A venogram made at this time showed a collateral circulation similar to the one shown in figure 10; this one had been made in November, 1944.

#### DISCUSSION

The clinical course of the first patient is of especial interest. The mechanism by which the original putrid lung abscess developed is an open question. The abscess may have developed in the pulmonary parenchyma by direct extension from a caseating mediastinal node. Reports of postmortem examinations of such cases have been described in the literature. Ordinarily, a complicating pulmonary suppuration in mediastinal tuberculous lymphadenopathy occurs through perforation into a bronchus. But this patient had no symptoms suggestive of a bronchial perforation. Furthermore, when a bronchial perforation does occur, a tuberculous pneumonitis is the usual result, not a putrid abscess of the lung. That the infected area found at the second operation was thought to be in the mediastinum gives credence to the "direct extension from the mediastinum" theory. Unfortunately, neither bronchoscopy nor examination for tubercle bacilli was made at that time.

The development of an esophago-bronchial fistula followed by a pulmonary abscess and pleural perforation as a result of tuberculous lymphadenopathy is uncommon. But the spontaneous complete closure of the fistula with survival of the patient is a rarity. A survey of the literature does not reveal any record of such a case. Emphasis should be placed on the fact that the fistula had completely closed before the initial dose of streptomycin was given.

The second case is noteworthy because of the improvement after exploratory thoracotomy, and especially because of the regression of the Horner's syndrome. The circulatory improvement might have been due to an increase in collateral circulation, but the diminution in the involvement of the cervical sympathetic chain could only be based on a subsidence of the inflammatory process. Furthermore, to make a diagnosis of tuberculous mediastinitis from the biopsy specimen is unique. In all other recorded cases, only a diagnosis of a chronic fibrosing inflammatory process could be made. This case establishes the possibility of diagnosis during life on the basis of a clinical picture which requires differentiation from invasion of the anterior mediastinum by malignant neoplasms.

#### SUMMARY

1. The literature on tuberculous esophago-tracheo-bronchial fistula and tuberculous mediastinitis causing superior vena caval obstruction has been reviewed.
2. Two cases have been presented illustrating these clinical entities.

3. In one case, the tuberculous lymphadenitis first resulted in a putrid lung abscess and then, after a considerable period of time, produced an esophago-bronchial fistula. This was complicated by a contralateral putrid lung abscess, with pyopneumothorax which was drained. The fistula closed spontaneously, an unusual occurrence. The clinical course has been chronic and benign with tendency towards lasting improvement.

4. In the second case, exploration for an anterior mediastinal mass causing superior vena caval obstruction disclosed a diffuse inflammatory process. Pathological examination of the biopsy specimen revealed tuberculosis. Improvement followed the operative procedure for no apparent reason. Later there was partial return to the preoperative state.

5. These cases illustrate a benign chronic form of tuberculous mediastinitis and mediastinal lymphadenitis. They establish that the diagnosis can be made during life even in the fibrosing variety.

6. Surgical measures, inadvertent or planned, directed towards the complications of chronic tuberculous mediastinitis and mediastinal lymphadenitis may offer considerable relief and even lasting improvement. They ranged in the reported cases from exploratory thoracotomy to drainage of a putrid pulmonary abscess and a putrid pyopneumothorax.

#### SUMARIO

##### *Mediastinitis y Linfadenitis Mediastínica Tuberculosas Crónicas*

1. Repásase la literatura relativa a la fistula esófago-tráqueo-bronquial y a la mediastinitis tuberculosa que ocasionan obstrucción de la cava superior.

2. Preséntanse dos casos típicos de dichas entidades clínicas.

3. En un caso, la linfadenitis tuberculosa dió, primero, por resultado un absceso pulmonar pútrido, y después, al cabo de un considerable período de tiempo, produjo una fistula esófago-bronquial, que se complicó con un absceso pulmonar pútrido contralateral, con pnoneumotórax que fué canalizado. La fistula se cerró espontáneamente, lo cual es raro. La evolución clínica ha sido crónica y benigna, con tendencia hacia una mejoría duradera.

4. En el segundo caso, la exploración de una tumefacción del mediastino anterior que obstruía la cava superior reveló un proceso inflamatorio difuso. El examen patológico del ejemplar obtenido en la biopsia reveló tuberculosis. Después de esta intervención se presentó mejoría sin razón aparente, pero después hubo un retorno parcial al estado preoperatorio.

5. Estos casos constituyen ejemplos de una forma benigna crónica de mediastinitis y linfadenitis mediastínica tuberculosas, sirviendo para establecer que puede hacerse el diagnóstico durante la vida aun en la variedad fibrosa.

6. Las medidas quirúrgicas, ya fortuitas o meditadas, dirigidas contra las complicaciones de la mediastinitis y la linfadenitis mediastínica tuberculosas crónicas, pueden aportar considerable alivio y hasta mejoría duradera. En los casos comunicados variaron las mismas de la toracotomía exploradora al drenaje de un absceso pulmonar pútrido y de un pnoneumotórax pútrido.

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# THE AMERICAN ASSOCIATION FOR THORACIC SURGERY

A Report of Its Meeting on May 28, 29 and 30, 1947<sup>1</sup>

RICHARD H. MEADE, JR.<sup>2</sup>

The first subject of great importance to be taken up at the recent meeting of the American Association for Thoracic Surgery was that of carcinoma of the lung. Although great advances have been made in recent years in the surgical technique of pneumonectomy, too many patients are found who have inoperable lesions. Anything which contributes to earlier recognition is of great importance. In the paper on *The Diagnosis and Operability of Bronchogenic Carcinoma*, by Gibbon, Clerf, Herbut and DeTuerk of Philadelphia, it was reported that in 118 proven cases of bronchogenic carcinoma only in 45 per cent were positive bronchoscopic biopsies obtained. However by studying, by the Papanicolaou technique, the stained bronchial secretions, the percentage of correct diagnoses was increased to 89. This low figure for positive bronchoscopic diagnoses was shown to be the generally accepted figure at the present time. Brewer, Wilfred Jones and Dolley found this identical figure in their study of 300 cases of lung carcinoma; and Grow and Bradford, in their study of 100 proven cases of carcinoma of the lung, found that in only 43 per cent were the lesions accessible to the bronchoscope. Burford and Wandall of St. Louis reported that a correct diagnosis of carcinoma had been established in 28 of 29 proven cases of carcinoma of the lung just from careful study of the sputum stained with hematoxylin and eosin.

The treatment of inoperable bronchogenic carcinoma by Methyl-bis was presented by Skinner, Carr and Denman. This drug which is a nitrogen mustard gas compound has been used experimentally since June, 1946 in 29 cases. In 70 per cent there was definite clinical improvement, with alleviation of pain the most frequent good result. Other reports gave a much smaller incidence of improvement.

The importance of exploratory thoracotomy for questionable shadows in the chest was brought out in the paper of Brewer, Wilfred Jones and Dolley, entitled *Non Malignant Lesions of the Lung Simulating Bronchogenic Carcinoma: Report of 50 Cases*; and in the paper by Grow and Bradford on *The Place of Exploratory Thoracotomy in the Management of Intrathoracic Disease*. With the increase in the ability to diagnose carcinoma from study of bronchial secretions and sputum when the lesion is not accessible to the bronchoscope the need for exploration to make the diagnosis in such cases will become increasingly less important. However, there still remain many other tumors and lesions which need surgical removal which cannot be identified except at operation.

<sup>1</sup> Presented before the Medical Section at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 18, 1947.

<sup>2</sup> Secretary, American Association for Thoracic Surgery, (1935-1947), 55 East Washington Street, Chicago 2, Illinois.

The importance of exploration for silent spherical shadows seen in X-ray films of the chest was emphasized by Edgar Davis in a report of 40 such cases. Malignant tumors were found in 70 per cent of these. Graham advocated resection of all large masses thought to be tuberculomata, because of the danger of overlooking a malignant tumor or because of the danger of there being a spread of the disease at a later date.

In regard to operability it was generally agreed by Gibbon *et al.*, the other essayists and the discussors, that pneumonectomy was the operation of choice for carcinoma and that resection should be undertaken in all cases in which all of the gross tumor tissue could be removed even if it had extended beyond the lung itself.

The studies of Neuhof and Aufses, and of Ralph Adams on the relationship between topography and histological structure and prognosis in carcinoma of the lung were reported. The former authors studied 52 cases of carcinoma of the lung in which there had been survival following resections during the period between 1935 and 1945. Their findings showed that a larger percentage of the patients with circumscribed tumors survived than of those with tumors grossly involving bronchi. No definite relationship between cell type and survival was apparent. All recurrences and metastases occurred during the first two years after operation. Ralph Adams reported a study of 48 cases in which there had been survival following resection prior to 1946. He found that the cell type was of great importance in regard to the duration of life. Of 15 patients surviving more than one year, 13 had epidermoid carcinoma. No patient with oat cell or undifferentiated carcinoma survived more than two years. In regard to the type of resection that gave the better results no definite conclusion could be reached by Adams, as in his series the results were about equally good from lobectomy and pneumonectomy.

Long survival after pneumonectomy for carcinoma was demonstrated by Doctor Graham when he presented the first patient who had ever recovered from such a procedure done for carcinoma. This patient had been operated upon by Doctor Graham in April, 1933 and had since then been actively engaged in the practice of obstetrics. He also presented 5 other patients upon whom he had done pneumonectomies six or more years before and all of whom had, since then, been living normal lives without evidence of recurrence. Of 53 patients on whom he had done pneumonectomies prior to 1942, 15 were now alive and well, although in 5 of them at the time of operation there had been lymph node involvement.

Lung abscess was discussed in two papers by Shaw and Paulson, and by Kent and Ashburn. The former authors reported the results obtained in the treatment of 86 cases by drainage and by resection. In 1942, Shaw reported 20 cases for which drainage was done in 18 and resection in 2 with a fatality rate of 15.2 per cent. Since then 66 more cases had been surgically treated and in this group there had been 48 resections with a reduction in the fatality rate to 5 per cent. In 1942 only 57.6 per cent were considered cured, whereas at the present time 80 per cent have been cured. Kent and Ashburn had had a similar



experience and reported 23 consecutive cases of chronic lung abscess treated by resection with a fatality rate of 8.6 per cent and with only one postoperative empyema. In 15 cases there had been multiple abscesses. All speakers emphasized the importance of not prolonging medical treatment of acute abscesses after improvement had ceased. The simple drainage of acute abscesses is very satisfactory but the chronic type requires more radical surgery. In the discussion of these papers it was pointed out that carcinoma should always be suspected in the chronic upper lobe abscesses and in all having insidious onsets, and that these should be treated by resection. In all cases it was thought wise to remove pieces of the abscess wall for histological study because of the possible association with carcinoma. In the medical treatment of lung abscess it was pointed out by Edwin Grace that the effectiveness of aerosol penicillin and streptomycin therapy could be enhanced by having the droplets of optimum size and by the addition of detergents. These important factors had been discovered as the result of war studies on increasing the effectiveness of certain poisonous gases. Zephyran chloride had been the detergent most often used.

W. E. Adams and Kershner read a paper on *Chronic Non-Specific Pneumonitis* and reported 10 cases. The condition is characterized by a diffuse chronic inflammatory process with marked fibrosis, lymphocytic and plasma cell infiltration associated with narrowing of the bronchi and atelectasis. No intra-bronchial lesion was found and no specific organism was isolated. Virus studies were not made. The symptoms developed insidiously and were productive cough with episodes of hemoptysis accompanied by low grade toxemia. X-ray films showed ill defined opacities extending out from the hilum without cavitation and occurring in one or both lungs. The differentiation from carcinoma is difficult at times. The process can be treated successfully by resection. Of the cases reported, the first 2 were treated by partial cautery resection, 7 by lobectomy or pneumonectomy and one bilateral case had a biopsy done. Other similar cases were reported by Robert Janes, Brodie Stephens, Bettman and Meade.

The subject of *Arteriovenous Fistula of the Lung* was presented by H. C. Maier, Himmelstein, Riley and Bunim. A case of arteriovenous fistula of the right lung associated with bacterial arteritis and contralateral empyema was reported in which cure had been secured following chemotherapy and lobectomy. The great value of angiocardigraphy in establishing the diagnosis was emphasized. Sweet reported 3 cases of middle lobe arteriovenous fistula and other cases were reported by Shefts, Byron, Bisgard and Abbott. John Jones reported a case at the 1944 meeting. Later in the meeting, Alfred Goldman of St. Louis read a paper on the hereditary features of this condition and reported the occurrence of the condition in 2 brothers. Its association with congenital telangiectases in half of the cases reported was emphasized.

The treatment of intrathoracic aneurysms by wrapping them with cellophane was reported by Osler Abbott. He had used polythene cellophane to produce fibrosis in 11 cases of intrathoracic aneurysms with most encouraging improvement in all. Angiocardigraphy has proved of great value but kymography has not. In patients with severe tracheal compression, preliminary decompression

under local anesthesia with no intratracheal tube, to avoid its irritating effects, was done. No bony structures were removed so as to avoid, as far as possible, the production of paradoxical movement.

Cancer of the esophagus was discussed by Strieder in a paper entitled *Surgical Management of Carcinoma of the Lower Two-thirds of the Esophagus and Cardiac End of the Stomach*. In exploring 87 patients he was able to do resections in 47 with survivals in 21. Sweet reported the experience with cancer of the esophagus at the Massachusetts General Hospital where 213 cases had been explored and resections done in 141 with survivals in 119; 32 patients were alive and well three or more years after operation, 9 for more than five years. William Adams reported that some 60 resections were done at the University of Chicago with a fatality rate of  $30 \pm$  per cent and these deaths have been due mainly to cardiovascular disease. As an example of the occasional long survival in patients with far advanced disease subjected to radical surgery, he reported that one patient with metastases to the cardiac nodes when operated upon nine years ago was still alive and well. W. A. Hudson said that he had one patient still alive with a functioning gastrostomy twelve years after esophagectomy and gastrostomy for an advanced carcinoma of the upper esophagus. It was generally agreed that a resection with immediate anastomosis of the mobilized stomach to the upper esophageal stump should be done in every case in which it was technically possible to do so, regardless of the extent of the disease, as it is the best form of palliative as well as curative treatment.

Willis Potts reported his experiences with aortic-pulmonary anastomosis for pulmonary stenosis. He had explored 33 patients and in 29 anastomosis had been accomplished. Four patients had died (13.8 per cent fatality). Out of the last 25 survivors, 24 were markedly improved and one slightly improved. In discussion the figures of Blalock were presented for his treatment of pulmonary stenosis. He had operated upon 415 cyanotic babies with a fatality of 14 per cent. In 283, a subclavian-pulmonary artery anastomosis had been accomplished with 10 per cent fatality.

Bradshaw, O'Neill and Hightower read a paper on *Resection of a Coarctation of the Aorta followed by Subclavian-aortic Anastomosis*. Crafoord and Gross had previously reported the successful resection of a coarctation of the aorta with end-to-end anastomosis. Blalock, in experimental work on dogs, had shown the feasibility of subclavian aortic anastomosis after resection of a part of the aorta. In Bradshaw's case, following resection of the coarctated segment there had been too long a gap to permit end-to-end anastomosis. He then made an anastomosis between the subclavian and the distal segment of the aorta. Although the patient died of pulmonary complications the anastomosis had functioned. In discussion it was reported that Clagett had done 3 such operations with success and in a fourth case of incomplete coarctation he had made a lateral anastomosis between the aorta and the subclavian artery. Julian Johnson reported 2 successful cases and Barkley and Davidson one each. Brodie Stephens demonstrated the value of diodrast injection into the common carotid artery for X-ray visualization of the coarctation.

The subject of congenital esophago-tracheal fistula and esophageal atresia

was introduced by the paper of Clayton Lyon and Stanley Johnson. In discussion, Cameron Haight reported on the experience at Ann Arbor. Forty patients had been operated upon and anastomosis accomplished in all. Twenty-two had died and 18 recovered. The last 6 patients had survived. The right extrapleural approach has been used in all cases. Logan Leven, the first person to successfully operate on one of these cases, reported that he had seen 42 cases and had done anastomoses in 17 with 10 survivors now alive. He also favors the extrapleural approach. Byron reported one case in which it had been necessary to bring up the mobilized stomach into the chest for anastomosis, with success.

*Esophageal Hiatal Hernias of the Short Esophagus Type* was the title of the paper presented by Olsen and Harrington. Two hundred and twenty patients with this condition had been seen at the Mayo Clinic in the last ten years. In 75 per cent there had been the symptom of obstruction to swallowing. In the establishment of the diagnosis it is important to obtain a biopsy through the esophagoscope to determine the height of the gastric mucosa. In many patients there was a stricture at the esophago-gastric junction. The authors felt that only a rare case was due to a congenitally short esophagus, the shortening being due to inflammatory changes in the vast majority. In cases having associated strictures, esophageal dilatations and medical measures have worked well. In many it has been necessary to reattach the diaphragm at a higher level and in some the induction of phrenic paralysis has been of value.

*Dorsal Sympathetic Ganglionectomy for Intractable Asthma* was reported by Duane Carr and Hughes Chandler. Five patients with true bronchial asthma, who had been completely incapacitated, had had bilateral resections of their upper dorsal sympathetic ganglia three to ten years ago and were now leading normal lives. Two of these had occasional mild attacks associated with upper respiratory tract infections. Archibald Grace reported that he had done posterior pulmonary plexus resections in 11 cases according to the technique of Rienhoff. Three had been dramatically cured and 8 had improved. He and Osler Abbott felt that resection of vagal fibres to the lung was more important than resection of sympathetic fibres.

Robert Bloch and associates reported on the experimental study of the effects of chemotherapeutic agents on the growing tubercle. Streptomycin was the most efficient agent studied. In view of the large number of papers to be read at this meeting on the various effects of streptomycin, nothing further will be recorded here of this interesting and valuable work.

Day, Chapman and O'Brien presented an analysis of 1,000 consecutive operations of closed intrapleural pneumonolysis. These operations were done on 923 patients and in no instance was death directly attributable to the operation. An effective pneumothorax was obtained in 46.8 per cent of the patients. The total incidence of empyema was 5.3 per cent including late as well as early cases. The greatest number of complications followed incomplete division of the adhesion. Among the absolute contraindications are: wide adherence of the lung to the chest wall and adhesions attached to peripherally placed cavities.

Welles and Gordon in their paper on *Preliminary Anterior Chondrocostectomy*

*Combined with Closed Cavity Drainage and Posterior Thoracoplasty* reported success with this method in the treatment of giant cavities. No other single procedure or combination of them had been effective. At the first stage an anterior chondrocostectomy is done. Two to three weeks later a drainage tube is inserted through this area into the cavity and closed suction drainage established. A month later a posterior thoracoplasty is done. In no case has cavity closure failed to be accomplished although some are still wearing a drainage tube. Streptomycin has been used by the intramuscular route only as examination of the cavity fluid has shown the presence of an appreciable concentration of the antibiotic.

Three important papers reporting on experimental work were presented. Robert Eaton of Grand Rapids was awarded the Rose Lampert Graff prize for his article entitled *Pulmonary Edema: Experimental Observations on Dogs following Acute Peripheral Blood Loss*. In experiments on dogs, he showed that an acute loss of 25 per cent of the total blood produced definite changes in the lung and in the circulatory balance. The most important change noted was pulmonary edema. This finding is of real clinical significance and emphasizes again the great importance of prompt replacement of blood lost during an operation.

Samuel Thompson read a paper on *The Effect of Pulmonary Inflation and Deflation upon the Maintenance of Circulation*. In this work he was able to demonstrate that the active inflation and deflation of the lung produces an artificial circulation, in the normal direction, over the entire body without the benefit of any heart activity.

A most dramatic piece of experimental work was reported by Rollin Daniel, Jr. in his paper entitled *The Regeneration of Defects of the Trachea and Bronchi: An Experimental Study*. Using dogs, Daniel resected segments of the trachea and bronchi, 2 to 4 cartilaginous rings in extent, and reestablished continuity of the tract by the use of vitallium, steel or glass tubes held in place by encircling ligatures of silk. Animals were sacrificed at intervals from two weeks to one year. They tolerated the tubes well and when sacrificed it was found that there was definite evidence of regeneration of cartilaginous rings and of the lining epithelium. Even at two weeks there was evidence of this regeneration and at the end of a year the process had long been complete. In several dogs he resected the right lung, lower end of the trachea and the upper end of the left primary bronchus and used a glass tube with which to bridge the defect between the trachea and the lower part of the left primary bronchus. Two of these dogs survived and were sacrificed at six months and fourteen months. In the second dog the tube became loose and was removed bronchoscopically at the end of six months. Autopsy studies showed complete regeneration of the cartilaginous rings and of the epithelium. This work, combined with the clinical experience of many in regard to the amazing repair of damaged bronchi, further extends the field of thoracic surgery and shows the possibility of resection of certain high-lying tumors previously considered inoperable.

A most important instrument was demonstrated by James Elam at Barnes

*Hospital.* This is an oximeter. By means of an attachment to the lobe of the ear this instrument can graphically record changes in the oxygen saturation of the circulating blood. Thus can changes be noted long before they become clinically manifest.

In conclusion, I should report, for those who may be interested, that the Association voted to accept the recommendations of the American Board of Surgery for the establishment of a subsidiary Board of Thoracic Surgery. Men who wish to be certified by this Board will first have to satisfy the requirements of the American Board of Surgery. The new Board should begin functioning by the autumn of 1948.

# THE CHEMOTHERAPY OF PULMONARY TUBERCULOSIS<sup>1</sup>

JOHN A. KOLMER<sup>2</sup>

Because of its high incidence and importance, pulmonary tuberculosis was among the first of the bacterial diseases to command attention from the standpoint of chemotherapy. This was also due to the ease with which well controlled experimental tuberculous infections could be produced in guinea pigs and rabbits suitable for chemotherapeutic investigations, bearing not only upon the discovery of chemical agents capable of exerting tuberculocidal or tuberculostatic activity *in vivo* without marked or serious toxic effects upon the host, but also upon the discovery of compounds capable of exerting dynamogenic or chemotactic effects upon tubercles and mineralization of the lesions.

As a result of extensive clinical and experimental investigations a large number of various synthetic dyes, as well as iodine and compounds of iodine, arsenic, copper, gold, cresosote, guaiacol, cinnamic acid, etc., have been studied. But while some of these appeared to exert suppressive effects upon tuberculous infections, there was no real encouragement until 1938 when Rich and Follis (1) showed by properly conducted experiments that the oral administration of sulfanilamide possessed limited but definite ability to retard the rate of development of experimental tuberculosis in guinea pigs. Since then, even more encouraging results have been observed in the treatment of experimental tuberculosis with diaminodiphenylsulfone and its derivatives (promin, diasone and promizole) and particularly with streptomycin; but before passing them in review along with the results observed up to the present time in the treatment of pulmonary tuberculosis it may be advisable to refer briefly to some of the basic principles involved.

## BASIC PRINCIPLES

Certainly both caution and conservatism are essential in appraising the specific chemotherapy of a disease like pulmonary tuberculosis because of the possibility of spontaneous improvement in many cases with or even without rest and adjuvant measures. Furthermore, the disease in human beings pursues an insidious course and often does not produce signs and symptoms until irreversible destructive and reparative changes have been produced in the tissues, requiring surgical intervention. In the final analysis actual healing must be accomplished by the slow processes of resorption, fibrosis and calcification with the chief rôle of specific chemotherapy confined to the prevention of extension of the infection while these mechanisms are in operation.

Needless to state the compound or compounds employed should possess a high degree of bactericidal or bacteriostatic activity for human and bovine tubercle

<sup>1</sup> Presented before the Maryland-District of Columbia Chapter of the American College of Chest Surgeons; Baltimore, Maryland, April 21, 1947.

<sup>2</sup> Research Institute of Cutaneous Medicine, 2101 Pine Street, Philadelphia 3, Pennsylvania.

bacilli *in vitro*, which should be highly specific or selective and not merely in the nature of general protoplasmic poisons. Hitherto it has been surmized that the waxy sheaths of tubercle bacilli protected them against chemotherapeutic attack, but the importance of this factor has probably been overemphasized, since it now appears that to be effective *in vivo* it is not necessary for a compound to kill the bacilli, as merely to cripple certain metabolic activities concerned in their proliferation or pathogenicity may suffice for chemotherapeutic purposes. Compounds should, however, possess sufficient bacteriostatic activity *in vivo* not only to suppress lesions but to reverse progressive destructive ones to a non-progressive state with ultimate resolution and encapsulation, as well as to eliminate bacilli from the organs and tissues of predilection to prevent the subsequent activity of possible latent infections.

Undoubtedly the character of the lesion or lesions is of great importance. Thus the ideal chemotherapeutic compound should be sufficiently diffusible not only to penetrate old, encapsulated avascular tubercles, but phagocytic monocytes and epithelioid cells as well, for the crippling or destruction of living tubercle bacilli within them. Unfortunately this ideal has not yet been completely attained, as both the sulfone compounds and streptomycin have proved much more effective in the treatment of early exudative lesions with a minimum of necrosis and encapsulation than in that of chronic lesions with massive necrosis and peripheral fibrosis. For this reason, the chemotherapy of acute early tuberculosis of guinea pigs and rabbits offers many contrasts to the treatment of the majority of tuberculous infections in man. Otherwise, the penetrability of these compounds for tubercles has not been definitely determined but, since it is well known that iodine possesses a high degree of penetrability, one naturally wonders whether it may not be possible to produce combination compounds of iodine and the sulfones or combination compounds of iodine and streptomycin with the hope of aiding in the solution of this important basic problem. Quite aside from this factor of penetrability of chronic lesions, however, chemotherapeutic compounds may be helpful without high penetration in the prevention of daughter tubercles and the dissemination of tubercle bacilli by the lymph and blood while specific resistance and reparative processes are being mobilized.

Needless to state, since the nature of pulmonary tuberculosis, especially of chronic infections, is such that prolonged chemotherapeutic treatment is to be expected or required, it is axiomatic that the compound or compounds employed should be well tolerated without serious or irreversible toxic effects in therapeutically effective doses over relatively long periods of time. From this standpoint the sulfone compounds promin and diasone have been found inferior to streptomycin, especially from the standpoint of producing hemolytic anemia, although promizole is much less toxic; furthermore, prolonged treatment with therapeutically effective doses of streptomycin carries the risk of producing irreversible damage of the auditory nerves with tinnitus and vertigo. For this reason it is greatly to be hoped that other nontoxic antibiotic agents of therapeutic value will be discovered for alternate use when prolonged treatment is required and since, according to Waksman (2), 20 to 40 per cent of all the *Acti-*





drainage, pneumonolysis and especially apicolysis, thoracoplasty or resections of the lungs. -

#### SULFONE COMPOUNDS

Such derivatives of diaminodiphenylsulfone as promin, diasone and promizole, however, have given more encouraging therapeutic results, although falling far short of original hopes and expectations. They are certainly inferior to streptomycin in the treatment of both experimental infections of guinea pigs and rabbits and of tuberculosis of human beings. Whether or not the oral administration of these compounds, especially promizole, will prove therapeutically helpful along with intramuscular injections of streptomycin as a form of synergistic or additive treatment cannot be stated at the present time although, as previously mentioned, the results observed in the treatment of experimental tuberculosis would appear to warrant the clinical trial of such combination therapy.

*Promin:* Undoubtedly promin has shown far more suppressive effects in the treatment of experimental tuberculosis of guinea pigs than the sulfonamide compounds (16 to 20). Unfortunately, however, human beings do not tolerate the compound by oral administration in doses sufficient for maintaining adequate blood concentrations as well as guinea pigs. Hemolytic anemias of varying severity have been observed although mild anemia does not appear to hinder the suppressive therapeutic effects of the compound upon tuberculous lesions.

Encouraging therapeutic results have been observed in the treatment of some cases of early exudative lesions of human tuberculosis following the oral administration of the compound (21, 22) although it has been reported as ineffective by intravenous injection (23). Little or nothing of therapeutic value, however, has been observed or expected in the treatment of pulmonary tuberculosis with caseation, necrosis, cavitation and fibrosis. Certainly promin has proved much less effective and more toxic than streptomycin with the result that it is not generally regarded as a practical remedy in tuberculosis.

*Diasone:* Diasone has also proved more effective in the treatment of guinea pigs infected with human tubercle bacilli than the sulfonamide compounds (10, 11, 24, 25) but has been reported as ineffective in the treatment of rabbits infected with bovine bacilli (25). According to Corper and Cohn (25) its therapeutic activity is largely due to the production of anoxemia and in direct relation to its cyanotic effects upon the spleen, liver and other internal organs. An early report by Petter and Prenzlau (26) on the results of treatment of pulmonary tuberculosis was favorable and encouraging but according to Hinshaw and his colleagues (27) these results have not been confirmed or convincing. Furthermore, the compound is also capable of producing anemia and other toxic manifestations in doses of 1.0 to 2.0 g. per day by ingestion as well as allergic reactions due to acquired sensitization (28).

*Promizole:* Promizole has likewise proved more effective in the treatment of experimental tuberculosis of guinea pigs than the sulfonamide compounds (16, 29, 30). Its value in the treatment of pulmonary tuberculosis, however, cannot be stated at the present time except to mention that it has apparently proved

more effective in the treatment of tuberculosis of the skin, lymph nodes, sinuses, etc., than of the lungs (27, 31). It is distinctly less toxic than promin or diasone due in part to the fact that it is conjugated in the body into a soluble compound readily excreted by the kidneys. In guinea pigs it has been observed to produce reversible parenchymatous hyperplasia of the thyroid gland (28, 29) although these effects have not been observed in human beings (27).<sup>3</sup> In the latter, however, large doses like 12 to 16 g. per day by ingestion may produce severe anorexia with upper abdominal pain and, while hemolytic anemia apparently does not occur unless very large doses are administered, yet acquired allergic sensitization to the compound has likewise been observed.

### STREPTOMYCIN

Undoubtedly streptomycin has proved the most effective agent yet discovered in the treatment of experimental tuberculosis of guinea pigs, although its ultimate evaluation in the treatment of clinical tuberculosis is both difficult and long delayed. Consequently, only tentative conclusions are permissible at the present time, except to state that it cannot qualify as the long awaited ideal chemotherapeutic agent. However, while streptomycin is not the first, nor likely to be the last, of compounds possessing chemotherapeutic activity in tuberculosis, present knowledge definitely indicates that future progress is likely to be in the antibiotic field.

*Experimental tuberculosis:* To Feldman and Hinshaw (32) belongs the credit for discovering the high therapeutic effectiveness of the compound in the treatment of experimental tuberculosis of guinea pigs following inoculation with various strains of human tubercle bacilli and of rabbits with bovine bacilli. Streptomycin, therefore, is not strain specific, which is very fortunate in relation to the treatment of tuberculosis of both adults and children. These investigators have found the compound capable of exerting marked and sometimes striking suppressive effects, although in most instances complete disinfection was not obtained with the result that living bacilli escaping destruction were capable of producing recurrent tuberculous infections upon the discontinuance of treatment. Essentially similar results have been observed by Smith and McClosky (4) in the treatment of experimental tuberculosis of guinea pigs and rats, by Youmans and McCarter (33) in the treatment of experimental tuberculosis of mice, and by Callomon, Kolmer, Rule and Paul (5) in the treatment of experimental tuberculosis of guinea pigs. Certainly it may be stated that no other agent so far investigated, including the sulfonamide and sulfone compounds, has shown as striking and encouraging results, amply justifying the hope that streptomycin may find a definite place of value in the treatment of clinical tuberculosis.

*Pulmonary tuberculosis:* Hinshaw, Feldman and Pfuete (34, 35), in reporting upon the treatment of 32 cases of active progressive nonsurgical tuberculosis of the lungs in adults, with 1.0 to 3.0 g. of streptomycin per day over periods of

<sup>3</sup> Milgram *et al.* (Am. Rev. Tuberc., February, 1947, 55, 144) have since reported such goitrogenic effects in children. [Editor]

two to six months, state that, while 5 succumbed, there was definite clinical and roentgenological evidence of improvement in 25 cases, although in 6 of these the disease became active with recurrent infection upon the discontinuation of treatment. Twenty-eight cases of the series had tubercle bacilli in the sputum or gastric contents before treatment and, of these, 13 became bacteriologically negative. Essentially similar results have been reported by McDermott (36) in the treatment of 12 cases of adult pulmonary tuberculosis, of 30 adult cases by Pfuetze and his associates (37), and of 4 cases occurring in young children by Sanford and O'Brien (38).

Best results have been observed in the treatment of hematogenous infections, especially early or moderately advanced cases of exudative pulmonary tuberculosis with or without thin-walled cavities. In such cases the results have been not only sometimes striking, but even dramatic, with prompt subsidence of fever, gain in weight, lowering of the sedimentation rate of erythrocytes and reduction in cough and expectoration, along with reversal of positive sputa to negative in from 30 to 40 per cent of cases. Unfortunately, however, much less effective results have been observed in the treatment of advanced cases of pulmonary tuberculosis with marked fibrosis and caseation necrosis.

All investigators are agreed that the therapeutic results were largely due to the suppression of the tuberculous infections preventing the development of new lesions but without complete or biological cure, since relapsing infections have been frequently observed upon the discontinuation of treatment and especially in cases with persistently positive sputa, uncollapsed cavities and those with emaciation and low natural resistance. In some instances, however, relapsing infections have been checked upon the resumption of treatment but always with the chances of failure due to acquired resistance of the tubercle bacilli to the compound. Indeed, it appears that the effectiveness of streptomycin in the treatment of tuberculosis consists in the prolonged suppression of the infection until encapsulation with mineralization has occurred.

Whether or not doses of 1.0 to 3.0 g. per day are required for these suppressive results cannot be stated at the present time. In this connection, it is greatly hoped that smaller daily doses will suffice, not only because of the high cost of streptomycin and the distinct risks of its toxic effects, but because it appears that the suppression of infection must be maintained for two to four months or longer until permanent arrest with adequate encapsulation has occurred. On the other hand, such prolonged treatment definitely increases the chances of therapeutic failure due to acquired resistance of tubercle bacilli to the compound. Consequently, until a newer substitute compound is available, it would appear that present large daily doses over one to two months may be the better plan in the treatment of early exudative cases of pulmonary tuberculosis at least.

Until dosage is more clearly and definitely defined, however, it is necessary to realize that streptomycin therapy is no substitute for other conventional forms of treatment of proved value. In view of its present high cost and potential toxicity, its administration should be postponed or denied cases making satisfactory progress toward arrest and reserved for the treatment of progressive

cases with or without surgical intervention. Nor has the intrathoracic injection of streptomycin alone or in conjunction with intermittent intramuscular injections proved of value in the treatment of 7 cases of tuberculous empyema (35), the unfavorable results being ascribed not only to the granulomatous nature of the disease, but to the fact that the exudates are usually acid in reaction whereas streptomycin is much more effective in a neutral or alkaline medium.

#### CHEMOPROPHYLAXIS

As previously mentioned, the oral administration of a sulfonamide compound, particularly sulfadiazine, has proved of some value in the prevention or control of pyogenic infections following lobectomy, pneumonectomy and other operations on the lungs and pleurae. This is particularly important in relation to ulceration of bronchial stumps following lobectomy in selected cases of unilateral tuberculosis after irreparable damage, such as bronchial stenosis or after an unsuccessful thoracoplasty, with contralateral spread of infection as the most common complication continuing to challenge the thoracic surgeon. For these purposes 1.0 g. of sulfadiazine may be given every four hours for a week before and one or two weeks after operation. Much better results, however, have been obtained by the intramuscular injection of 20,000 units of penicillin every three hours for a week before and one or two weeks after operation, and in the case of the prevention of ulceration of bronchial stumps with contralateral infection, I recommend that 40,000 units of penicillin be given every three hours along with 1.0 g. of sulfadiazine orally every four hours for a week or two after operation.

Streptomycin also possesses prophylactic value in connection with thoracic surgery including resection of the lung which has proved of value in the treatment of pulmonary tuberculosis by Brantigan (39) and other thoracic surgeons after the occurrence of irreparable damage and when the contralateral lung is free of disease. Thus it is capable of suppressing the rekindling of tuberculosis following surgical manipulations of tuberculous tissues after thoracoplasty, lobectomy, suction drainage of isolated cavities after thoracoplasty, open and closed intrapleural pneumonolysis, extrapleural pneumonolysis and especially apicolysis, the management of complications of pneumothorax, such as the tearing of adhesions, rupture of superficial cavities, etc. It is also advisable to administer streptomycin in cases subjected to thoracic surgery when intestinal tuberculosis is present; likewise in the treatment of nontuberculous pneumonia complicating pulmonary tuberculosis, for the prevention of reactivation of quiescent foci or an increase of tuberculous infection in active pulmonary tuberculosis.

#### SUMMARY

1. Streptomycin has been found the most effective agent so far discovered in the treatment of both experimental and human tuberculosis, although it cannot qualify as the long awaited ideal chemotherapeutic agent. Its therapeutic effects are largely due to the suppression of tuberculous infections with the prevention of new lesions but usually without complete or biological cure.

2. Promin and diasone are not generally regarded as practical remedies in tuberculosis. Promizole is much less toxic and worthy of clinical trial in conjunction with streptomycin as a form of synergistic or additive chemotherapy.

3. The sulfonamide compounds, penicillin and streptomycin, alone or in combination, have proved of chemoprophylactic value in thoracic surgery.

#### SUMARIO

#### *Quimioterapia de la Tuberculosis Pulmonar*

1. La estreptomicina ha resultado ser el agente más efectivo descubierto hasta la fecha para el tratamiento de la tuberculosis tanto experimental como humana, aunque no constituye el muy esperado elemento quimioterapéutico ideal. Sus efectos terapéuticos se deben en gran parte a la supresión de infecciones tuberculosas, unida a la prevención de nuevas lesiones, pero por lo general sin curación completa o biológica.

2. La promina y la diasona no están consideradas generalmente como remedios prácticos en la tuberculosis. El promizol es mucho menos tóxico y merece una prueba clínica, unido a la estreptomicina, en forma de terapéutica sinérgica o aditiva.

3. Los compuestos sulfonamidos, la penicilina y la estreptomicina, ya solos o combinados, han mostrado valor quimioprofiláctico en la cirugía torácica.

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# ANTIBIOTIC AND CHEMOTHERAPY OF TUBERCULOSIS<sup>1</sup>

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The remarkable accomplishments of chemotherapy during the past few years have brought this science to a high tide of achievement in the struggle between man and microorganisms that has gone on for centuries. But complete victory has not been attained. Many questions remain unanswered, many problems unsolved. One is the chemotherapy of tuberculosis.

Recently Hart (1) aptly wrote about the progress of chemotherapy: "In 1935, after 30 years of progress in the fields of protozoal and spirochaetal infections, but without chemical mastery of any important general *bacterial* infection in humans, a substantial part of the bacterial front was broken." While in agreement with Hart's statement, still one should recall that, so long as tuberculosis continues to be responsible for the death of millions of people throughout the world, a most important part of man's struggle against the infectious diseases remains to be achieved. It is also timely that we remind ourselves that the "present happy position in the prevention and treatment of sepsis has not been achieved by a flash of insight on anyone's part" (2). The major victories which have been achieved by the use of chemotherapy during the past *ten* or *twelve* years were made possible by the work and observations of a host of investigators in different parts of the world during the past *fifty* years.

The more recent brilliant accomplishments of chemotherapy in the general field of the infectious diseases have rekindled hope and renewed expectation that we will not "remain bankrupt in methods of *directly* attacking the tubercle bacillus" (3).

As one examines the history of the therapy of tuberculosis, one of the most arresting facts that stands out is that common human trait even among scientists, "overenthusiasm," for the many and varied therapeutic agents used in the treatment of this disease since ancient times. It is an interesting observation that this tendency on the part of some of the world's great scientists and clinicians has been largely responsible, on many occasions, for the profession at large following hopefully, if blindly, down long and tedious therapeutic highways which have often led to disillusionment and failure. The indiscriminate use of calomel for any and all ailments throughout the years, and the use of tuberculin during modern times, are illustrative of many examples which might be offered. Yet, it is probably equally true that this same enthusiasm combined with objective thinking and search for the truth is largely responsible for the present high-water mark of success in the field of chemotherapy.

<sup>1</sup> Presented in part by the senior author (H. M. R.) at the annual meeting of the Canadian Tuberculosis Association, Quebec, Canada, May 16, 1947, and at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 18, 1947.

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## PROBLEMS PRESENTED BY CHEMOTHERAPY

For many decades the idea that tuberculosis is somehow basically and radically different from other infectious diseases has plagued the progress of chemotherapy of this disease. That tuberculosis does differ from other infectious diseases in many important respects is to be emphasized anew, but that it is basically and fundamentally similar to other infectious diseases has been made clearer in recent years, partly as a result of the search for, and application of, new chemotherapeutic agents for these diseases. Continued studies along these lines may afford a still better understanding of many baffling aspects of this protean disease, of man's varied reaction to it, and of its etiological agent.

For example, it would be of the utmost importance to know *how* and *why* the tubercle bacillus has the rather unique distinction of producing caseation, necrosis and liquefaction; *why* characteristics and clinical patterns of the disease differ so profoundly in different animals and species, and in the same animal (man) at different ages and among different racial groups; *why* it is *acute* in some and *chronic* in others; *why* it tends to *localize* in some and *generalize* in others; *why* it *heals* readily in some and *progresses* rapidly in others; *why* it confers *relative* immunity in some and rapidly *destroys* others.

It would also be of great benefit if we better understood *how* and *why* certain infectious diseases may confer complete and lasting immunity, and others only relative, temporary, or at times apparently no significant immunity.

One is also led to inquire *how* and *why* one antibiotic (penicillin) may overcome such malignant infections as streptococcus septicemia, yet completely fail to influence beneficially the behavior of a small area of acute tuberculous lobular pneumonia. The successful use of penicillin against streptococcus septicemia and its failure against acute tuberculous lobular pneumonia, presumably demonstrates the chemical and biological specificity or selectivity of this antibiotic for the streptococcus, and its lack of specificity for the tubercle bacillus. The explanation of this selectivity on the part of certain antibacterial agents for certain microorganisms remains one of the important unsolved problems of chemotherapy.

Search also continues for a plausible explanation of *why* the inhibitory effect of antibacterial agents differs so profoundly *in vitro* and *in vivo*. Finally, the mode of action by which antibacterial agents retard, inhibit or prevent multiplication and growth of microorganisms is not completely understood (Wells (4) and Waksman (5)). Several different mechanisms of action have been propounded.

Ehrlich's explanation was based on the principle of selective affinity between bacteriostatic or bactericidal agents and the protoplasm of the microorganism. Waksman offers two illustrations of the possible mode of action of antibacterial agents: (a) "If a given substance interferes with the utilization by the bacteria of a certain metabolite in the medium, as in the relation of sulfa drugs, 2-p-aminobenzoic acid, one must assume that the sensitive bacteria require the metabolite in question, and the resistant forms do not, or that the resistant bacteria synthe-

size larger concentrations of the particular metabolite than the sensitive forms . . ." (b) Another possible mechanism is "the absorption of the antibacterial substance by the bacterial cell rendering the cell incapable of multiplying or dividing."

Although a better understanding of the mechanism of action of antibacterial agents is obviously not essential to the even greater success of chemotherapy, nevertheless, it would seem highly desirable to have it, particularly with regard to chemotherapy of tuberculosis.

The following comment well states the unusually favorable position of chemotherapy to-day, and adequately portends reasonable expectation for further success in this field. "Whether gramicidin or any other product of micro-bacterial origin will eventually be found to fulfill certain purposes better than either sulphonamides or any other class of antiseptic remains to be seen. That several classes of reagent should be competing for supremacy in different aspects of the task which not long ago was considered impossible of any real fulfillment, is a truly remarkable position" (6).

#### METHODS USED IN THE PAST

Precise knowledge of tuberculosis has accumulated largely during the past half century. Because of the previous lack of such knowledge, treatment of this ancient malady has been forever changing, usually empirically, and with limited success. The history of chemotherapy of tuberculosis has been no exception to this general rule.

Arsenical compounds have been used for consumption, or phthisis, since antiquity; iodine and iodides, first in the form of seaweed (Hart), since the time of the Salerno School (11th century); gold and mercury since the sixteenth century; cod-liver oil since about the seventeenth century and creosote since about the same time. Throughout the years, the use of these agents has remained empirical and highly controversial, and their mode of action conjectural.

The following concoction is illustrative of the empirical nature of tuberculosis therapy offered as recently as some two hundred years ago by that renowned author and clinician, Sir Richard Morton (7), "for the cure of consumption in the second degree." From its ingredients one might guess that it not only contained vitamins, but perchance even an antibiotic! It almost certainly was an unpleasant medicament.

"Take of new Milk two Gallons, distil it with Mint, Roman Wormwood, of each two Handfuls, to a Gallon. Then Take of Garden Snails, washed first in common Water, and then Small beer, half a Peck, of Earth-Worms slit and wash'd a Pint, of Angelica a Handful and half, Agrimony, Betony, Rue, of each a Handful. Put the Herbs in the bottom; upon these lay the Snails and Earth-worms, and upon the top of all lay of Shavings of Hartshorn half a Pound, of Cloves an Ounce, of Saffron three Drams, Infuse them in two Quarts of Syder, and a Quart of the best Malaga Sack, and then distil them in an ordinary Still. These Liquors must be drank plentifully."

Very little scientific study of the pharmacological, therapeutic and toxic effects of the numerous agents used for the treatment of tuberculosis was carried out prior to the present century. The only basis for the continued and often sporadic use of these and other substances was founded presumably on the usually untenable claim of "clinical impression." This is a critical, but apparently justifiable, indictment of clinicians and their methods of evaluating therapeutic agents and clinical results on such an unpredictable, protean, acute, subacute and chronic disease as tuberculosis.

Perhaps one of the most cogent reasons for the persistent, enthusiastic and often sporadic use of various therapeutic agents in the treatment of tuberculosis has been the failure of clinicians to heed the warning of Robert Koch (8), "that the success of an animal experiment gives no certain indication of the result of the same experiment upon a human being." Pinner (9) puts it even more succinctly commenting on the comparative effect of streptomycin and promin on tuberculosis in guinea pigs and man: "It is only a quantitative difference—and not a very marked one at that—in the antituberculosis action of promin and streptomycin in experimental tuberculosis in guinea pigs; but an essential and profound one in human tuberculosis. No preparatory animal work with streptomycin, as far as I know, revealed its toxic effect in man." And he concludes, "there is a *difference*, not only between *guinea pig* and *man*, but also between *tuberculosis in guinea pig* and *man*." (Italics the authors'.)

Obviously, past and present clinicians in their eagerness to find some effective chemotherapeutic agent for tuberculosis, have often erred in disregarding or overlooking this principle first enunciated by Koch more than half a century ago, and often repeated by many authors.

Zucker *et al.* (10) also draw attention to other important questions in the evaluation of new drugs for the treatment of tuberculosis. They emphasize that, when testing for the therapeutic action of any new drug, a definite beneficial effect should soon become evident in early, exudative lesions, and if no unusual improvement is noted in one to two months, the drug is probably not effective against clinical tuberculosis. These authors further emphasize that no elucidation may be expected by treatment and follow-up over many months because of the many variables in the natural course of the disease which will becloud the issue. They also warn against the pitfalls of depending solely upon control cases in testing new chemotherapeutic agents for tuberculosis since "such cases do not help to segregate such exceptional developments (remarkable improvement) unless hundreds of cases be observed."

During the latter part of the nineteenth century, rapid progress was being made in organic chemistry, pharmacology, physiology and experimental pathology. Bacteriology developed rapidly, aided by the uses of dyes to stain microorganisms which were being isolated from and identified with certain diseases. Koch had still not discovered that the tubercle bacillus was the cause of tuberculosis. However, Villemin had already demonstrated that tuberculosis was an infectious disease.

Lister and others were concerned with the problems of asepsis and antisepsis. Even in this prechemotherapeutic period, while bacteriology was still in its infancy, bacterial antagonism or antibiosis was being noted by Pasteur and Joubert (11) and others. In 1877, while working with anthrax bacilli, they observed that these organisms grew readily on neutral or slightly alkaline urine until the urine was "inoculated" with one of the "common bacteria" after which the anthrax bacilli showed little or no growth. In the same paper they reported that animals susceptible to anthrax infection could be protected from developing the disease by the simultaneous injection of some "common bacteria." They concluded that "these facts perhaps justify the highest hope for therapeutics."

It is of interest that this first bacterial antibiosis or antibiotic effect was observed some five years before Koch was to announce the discovery of the tubercle bacillus. Although Pasteur and Joubert apparently did not pursue their important observation further at the time, other investigators were soon to make similar observations. In 1885, Babès (12) demonstrated that certain microorganisms may produce substances which prevent or inhibit the growth of other bacteria *in vitro*. He, too, mentioned the potential therapeutic possibility of this antagonistic action of certain microorganisms.

In the same year (1885) Cantani (13) reported on the treatment of a tuberculosis patient with what he designated as *Bact. termo*, apparently a nonpathogenic organism, by having the patient inhale the contents of the bacterial culture by the use of an atomizer. Cantani claimed that *Bact. termo* replaced the tubercle bacillus in the sputum, and that the patient improved. This, so far as the authors are aware, is the earliest recorded use of aerosol bacterial replacement therapy.

At about the same time (1881) Robert Koch was one of the first to study chemotherapy in the experimental laboratory. After he had found that mercuric chloride inhibited the growth of anthrax bacilli *in vitro*, he treated guinea pigs infected with anthrax bacilli with this compound, but without success. Koch, Ehrlich and others were to continue their laboratory investigations of the chemotherapy of the infectious diseases, including tuberculosis, but largely without success until Ehrlich and Hata successfully treated syphilis with salvarsan (1910). These notable achievements, particularly of Ehrlich and his associates, marked the beginning of a new scientific era in chemotherapy. Koch having apparently become discouraged at not finding an effective chemotherapeutic agent for tuberculosis, turned his attention to the development of tuberculin for which he apparently had great hope as a therapeutic as well as a diagnostic agent.

The new interest and enthusiasm resulting from Ehrlich's discoveries aroused renewed expectation among some that a chemotherapeutic agent might be found effective for the treatment of clinical tuberculosis. This idea seemed to have been encouraged by the repeated demonstration that many drugs and chemical compounds inhibit the growth of tubercle bacilli *in vitro*, even in weak dilutions in many instances. However, despite Koch's warning previously referred to,

meability of tubercles and caseous tissue by chemotherapeutic agents. Corper (18) demonstrated that soluble salts of metals, when injected into animals, usually go into a colloidal state, and as a rule do not penetrate caseous tissue. However, Lewis (19) and DeWitt (20) found that trypan red, trypan blue and methylene blue entered caseous material when injected into experimental animals. They also tested out many compounds of dyes containing silver, copper or mercury against experimental tuberculosis, but without success.

Despite the success which had been claimed from time to time with *chaulmoogra oil* in the treatment of leprosy, Walker and Sweeney (21) did not find that the chaulmoogric acid entered tubercles, and their results on experimental tuberculosis in animals were essentially negative.

Although arsenical preparations were long used in the treatment of tuberculosis, Smith (22), and Arkin and Corper (23) found no significant inhibitory effect of *arsenic preparations* on tubercle bacilli *in vitro*, and the former also noted that they had no effect on tuberculosis in guinea pigs.

In 1890, Koch (24) demonstrated that *gold salts* inhibited the growth of tubercle bacilli *in vitro* even in weak dilutions. However, he also found that they were *ineffective* against tuberculosis in experimental animals. Despite Koch's findings, different gold salts have been used extensively, if sporadically, particularly on the European continent and to a less extent in South America and in other parts of the world, in the treatment of clinical tuberculosis. DeWitt, Cadwell and Leavell (25, 26) tested many of the gold salts which were being advocated and used clinically, and verified Koch's earlier findings. They concluded that none of the gold salts which they tested had any significant effect on experimental tuberculosis in guinea pigs. Following their work, the popularity of gold salts for the treatment of clinical tuberculosis again declined somewhat.

In 1924 Möllgaard (27) introduced a new gold salt, sodium aurothiosulfate or "sanocrysin," for the treatment of tuberculosis. It was claimed that this preparation would prevent the development of experimental tuberculosis in animals, and that it did not produce serious toxemic effects in man. It was also stated that it was especially effective for acute exudative tuberculosis. However, it was soon discovered that it caused serious toxemic reactions in man.

Amberson, McMahon and Pinner (28) published their results with sanocrysin in 1931. They treated 12 cases of pulmonary tuberculosis and also followed 12 controls. They administered the drug intravenously, each patient receiving a total of from 3.1 to 6.1 g. They concluded that sanocrysin had no beneficial effect on the disease, and that the control cases did as well or better than the treated cases. They also emphasized the dangers of toxicity of the drug, and stated that toxemic reactions were noted in all cases. One patient died as the result of parenchymatous degeneration of the liver, apparently caused by the drug. All patients showed evidence of temporary renal damage following the third or fourth injection. Other frequent toxemic effects were skin rashes, stomatitis, ocular irritation, nausea, anorexia and vomiting, diarrhea and jaundice. For reasons indicated, they concluded that the use of sanocrysin is not justified in the treatment of tuberculosis.

Wells (29) concluded that, although sanocrysin had some inhibitory effect on

the tubercle bacillus *in vitro*, it has no bactericidal effect even in concentration of 1:2,000. Despite the previous failures of other gold salts in the treatment of tuberculosis, a wave of unexplained enthusiasm followed Möllgaard's claims for sanocrysin, and between 1925 and 1936 sanocrysin was used extensively, particularly in European countries.

In this connection, Hart's comment in regard to gold therapy is not only of interest, but is timely in our present state of evaluating streptomycin. He writes: "This astonishing acceptance of a remedy, and its subsequent rejection without any immediate better substitute, is only equaled by the preceding, but overlapping, dramatic rise and fall of tuberculin therapy."

The history of the enthusiasm for tuberculin and gold therapy for the treatment of tuberculosis should have, and probably has had, a salutary effect on those now evaluating the usefulness and limitations of streptomycin for tuberculosis. It is of interest that the definite decline of gold therapy followed the peak of publication of papers dealing with its toxic effect.

The half century between 1885 and 1935 witnessed a constant ebb and flow of opinion regarding many different types of therapy of tuberculosis. The necessity for so many therapeutic agents and procedures for the treatment of any disease is significant, since it indicates the relative inadequacy of any one method.

With the demonstration that *sulfanilamide* and its derivatives were effective in the treatment of experimental and clinical streptococcus and other pyogenic infections, interest in these compounds for the treatment of experimental and clinical tuberculosis became aroused. Investigation (30) soon demonstrated that sulfanilamide and many of its derivatives inhibit the growth of tubercle bacilli *in vitro*. Studies of these compounds in experimental tuberculosis, however, revealed that they had little or no effect on the course of the disease even in large doses. They were also found to have no beneficial effect on the course of clinical tuberculosis.

In 1939, the sulfone compounds, synthetic preparations related to sulfa drugs, became available. The first of these compounds to be tested against experimental and clinical tuberculosis was *promin* or sodium p-1 diaminodiphenylsulfone-N, N-1 dextrose sulfonate. Feldman, Hinshaw and Moses (31) reported in 1940 that preliminary results indicated that promin inhibited the progress of tuberculosis in guinea pigs. Medlar and Sasano (32) (1943) also tested promin in the treatment of tuberculosis in guinea pigs, and concluded that promin definitely retarded the disease, but did not eradicate the infection. Steenken, Heise and Wolinsky (33) obtained similar results.

Hinshaw and his associates (34 to 40) reported on promin in the treatment of clinical tuberculosis between 1942 and 1944. They concluded that, "The results are sufficiently suggestive and encouraging to make it urgent that a series of large and fully controlled studies be done." They also mentioned undesirable toxic reactions which "are constantly to be coped with, but measurable, reversible and controllable." Anemia seemed to be one of the most frequent toxic manifestations. These authors also reported one case of agranulocytosis apparently due to the drug.

Zucker, Pinner and Hyman treated 12 patients with promin intravenously

and concluded that the drug "exerted no chemotherapeutic effect except possibly in one case of tracheobronchial tuberculosis." One of their patients developed an acute hemolytic anemia of moderate severity, and others experienced mild toxemic reactions.

Another sulfone compound, *promizole*, has also been studied extensively during the past few years, being tested both in the treatment of experimental and clinical tuberculosis. In 1944, Feldman, Hinshaw and Mann (41) reported that the drug exerted a deterrent effect on tuberculosis in guinea pigs, "slightly inferior to that of promin." It appears less toxic for human beings although it does produce reversible hyperplasia of the thyroid.

*Diasone*, also a sulfone compound, apparently exerts considerable favorable influence on tuberculosis in experimental animals but most clinical experience with this preparation has been disappointing.

The experience with the sulfone compounds again demonstrates the fact that chemotherapeutic agents may have a much greater antituberculosis effect on experimental tuberculosis in animals than on human tuberculosis, and less toxic effect on experimental animals than on man.

#### ANTIBIOTICS IN TUBERCULOSIS

Recently Waksman has pointed out that microbiologists and bacteriologists have long noted important interrelationships among microorganisms. Tyndall (42) in 1876 spoke of "the struggle which exists between the bacteria and the penicillium. The bacteria, which manufacture a green pigment, appear to be uniformly victorious in their fight with the penicillium." As previously mentioned, in 1877 Pasteur and Joubert observed that certain airborne bacteria inhibit the growth of anthrax bacilli *in vitro* as well as *in vivo*.

Duclaux (43) demonstrated that the growth of a fungus renders the medium unfavorable for future growth of the same organism, and Marmorek (44) showed that the growth of antagonistic streptococci in broth made the culture medium unsatisfactory for a later growth of the same organism. Microorganisms may be not only hetero-antagonistic, but also iso-antagonistic (Waksman).

Waksman reports three types of antagonisms: (a) repressive, inhibitive or bacteriostatic, (b) bactericidal and (c) bacteriolytic. He believes these antagonisms are due to the production of antibiotic substances by the antagonists. Waksman points out that antibiotic substances are selective in action and that conditions for the bacteriostatic activity of antibiotics vary greatly, and the mechanism of action is different. Some antibiotics interfere with cell division, others with bacterial respiration and others with utilization of essential metabolites.

It has been shown that a number of antibiotic agents have a bacteriostatic effect on the tubercle bacillus *in vitro* and some *in vivo*. According to Waksman and others, the following antibiotics exert a bacteriostatic effect on the tubercle bacillus *in vitro*: (a) actinomycin, (b) streptomycin, (c) filtrates from *A. fumigatus* cultures (active filtrate), and (d) from *A. albus*. Jennings (45) reported that fumigacin, a product of *A. fumigatus*, inhibits the growth of the tubercle bacillus

*in vitro* in dilutions of 1:10,000. Other antibiotic substances having an inhibitory effect upon the tubercle bacillus are the following: (e) pyolipic acid derived from *P. aeruginosa*, (f) streptothricin from *S. lavendulae*, (g) subtilin from *B. subtilis*, and (h) aspergillic acid from *A. flavus*. Waksman also states that filtrates of still other fungi have been found to have a definite antibacterial action against both human and bovine strains of tubercle bacilli *in vitro*.

Despite the fact that a number of antibiotic substances have been demonstrated to have an inhibitory effect on the growth of the tubercle bacillus *in vitro*, to date only one, streptomycin, has been found to have beneficial effects in the treatment of tuberculosis in man.

**Streptomycin:** In January, 1944, Schatz, Bugie and Waksman (46) announced that they had obtained an antibiotic substance they called streptomycin from the fungus *Actinomyces* (*Streptomyces*) *griseus*, and in November, 1944, Schatz and Waksman (47) reported that streptomycin exerted a bacteriostatic effect on a human strain of *Mycobacterium tuberculosis*. A short time later, Feldman and Hinshaw (48) demonstrated that streptomycin had a striking therapeutic effect on experimental tuberculosis in guinea pigs, apparently without causing any demonstrable toxemic reactions.

Hinshaw and Feldman began clinical trials with streptomycin on tuberculosis patients in the fall of 1944. Since that time, the Mayo Clinic and Foundation investigators (49 to 61) have had continuous experience with the drug in the treatment of practically all forms of clinical tuberculosis, although the number of cases treated of some of the less common varieties of the disease are still relatively few.

In 1946, Hinshaw, Feldman and Pfuetze (62) reported their observations and results on 100 cases of tuberculosis treated with streptomycin. Among these were patients with miliary tuberculosis and tuberculous meningitis, pulmonary tuberculosis, tuberculosis of the larynx and bronchi, empyema, cutaneous fistulae, tuberculosis of the genito-urinary tract, bones and joints, surgical pulmonary tuberculosis and miscellaneous types of the disease.

In the cases of miliary tuberculosis and tuberculous meningitis, 6 of the 12 treated patients had died at the time of the authors' report (1946). Of the 6 living patients, 4 were regarded as having "arrested" meningitis. Neurological disturbances were present in 3. One patient was blind, one deaf and the third had profound cerebellar dysfunction. The authors recommended that streptomycin be given by both the intrathecal and intramuscular routes for tuberculous meningitis, and stressed the importance of early and prolonged treatment with large dosage. They also pointed out the possibility of relapse even after apparent clinical arrest of the meningitis.

Thirty-two patients with "nonsurgical" pulmonary tuberculosis were treated; all had moderately or far advanced disease. Treatment was over a period of two to six months, and 1 to 3 g. of the drug was given daily. Results were reported as follows: (1) roentgenographic improvement in 25 patients; (2) cavity closure in 12; (3) sputum conversion in 13 (culture or guinea pig inoculation); and (4) 5 patients died.



Improvement was noted in 5 of 7 patients treated for ulcerative lesions of the respiratory tract (pharynx, larynx and large bronchi).

The results in 7 patients treated for tuberculous empyema were not encouraging. In 15 cutaneous fistulae, favorable results were noted within four to six weeks. However, the fistulae recurred in about one-third of the cases. The authors found streptomycin to have a palliative effect in tuberculosis of the bladder and kidney, but no curative effect was observed. Five cases of bone and joint tuberculosis were treated with improvement in 4. Streptomycin was also given preoperatively and postoperatively to 7 patients having pulmonary resection for pulmonary tuberculosis. The drug seemed to "contribute substantially" to the recovery of all 7 patients.

The authors concluded that, in many instances, streptomycin appears to suppress tuberculosis rather than eradicate it. Its action seems to be bacteriostatic rather than bactericidal. They also emphasize that toxemic manifestations may occur particularly when large doses are used over a long period of time. The most severe and frequent toxemic reactions, including deafness, seem likely to occur in patients with meningitis, requiring intrathecal as well as intramuscular injections.

Baggenstoss *et al.* (63) reported on the effect of streptomycin on the pathological lesions of miliary tuberculosis in 5 cases which came to necropsy. The authors state that there was convincing evidence of regression and healing in the miliary tubercles of the lung, liver and spleen in all cases except one. This case received treatment for only a few days. They described healing as the "occurrence of fibrosis, hyalinization and absence of caseation in the miliary tubercles." However, tubercle bacilli were demonstrated in the tubercles in 3 of the 5 cases.

McDermott (64) and associates recently reported on the results of 41 cases of pulmonary and miliary tuberculosis and tuberculous meningitis treated with streptomycin at the New York Hospital. They used highly purified streptomycin in large doses, and investigated particularly the toxemic effects of the drug. Their results closely parallel and confirm those reported earlier by Hinshaw and the Mayo group.

During the past year and a half, a large number of tuberculosis patients have been treated in hospitals of the Veterans Administration under the administrative leadership of Doctors John B. Barnwell and Arthur M. Walker. Recently a preliminary statement (65) of these studies and similar studies in the Departments of Medicine of the Army and the Navy concerning the effects of streptomycin on tuberculosis in man indicates that the therapeutic results obtained and toxic manifestations observed by these groups are quite comparable to those previously noted by the Mayo and Cornell groups.

Of unusual interest is the report on tuberculous meningitis treated by the Veterans group and read by Dr. Paul Bunn (66) as part of the streptomycin symposium presented at the 1947 annual meeting of the American Trudeau Society, Medical Section of the National Tuberculosis Association, (published in the *Am. Rev. Tuberc.*, November, 1947). Bunn reported that, of 71 patients

with tuberculous meningitis treated with streptomycin, approximately one-third died within six weeks after treatment was begun. However, 15 of the patients are now clinically well after completion of treatment and the spinal fluid is negative on culture for tubercle bacilli but still shows a high protein content and an elevated cell count. Two of the 15 patients are deaf. The remarkable results obtained by the Veterans Administration in this usually fatal type of tuberculosis indicate the possible salvage of approximately 21 per cent of patients so affected if treated early and adequately with streptomycin.

Stimulated by the encouraging results obtained by the Mayo and New York Hospital groups, the American Trudeau Society (67) undertook a large-scale streptomycin research project in the fall of 1946, being generously aided by the streptomycin producers<sup>3</sup> who donated a large amount of the drug to the Society, by the Research Grants Division of the National Institute of Health, U. S. Public Health Service and by the National Tuberculosis Association.

The results of the Trudeau Society investigators have not been published, but a preliminary report was given by several members of this group as part of the recent streptomycin symposium of the Society. These reports also closely parallel and confirm the earlier studies of the Mayo and New York Hospital groups.

One of the greatest disappointments thus far encountered in the streptomycin treatment of tuberculosis is the frequent tendency of the tubercle bacillus to become resistant to the drug when therapy is prolonged. Youmans (68) and his associates report that tubercle bacilli from 8 of 12 patients treated with streptomycin developed resistance to the drug 500 to 1,000 times as great as that of cultures taken before treatment. Further work on the development of resistance to the drug on the part of the tubercle bacillus is now in progress. It would appear at present that the early development of marked resistance of the tubercle bacillus to streptomycin, *in vivo*, might significantly limit the beneficial effects of the drug.

However, before the tubercle bacillus becomes resistant to streptomycin, the remarkable suppressive effect that the drug has been shown to have against both experimental and human tuberculosis, notably acute and ulcerative tuberculous laryngitis and bronchitis, and against the more acute and subacute exudative pulmonary lesions, and particularly its unprecedented effect on tuberculous meningitis and miliary tuberculosis, even though a great majority of these latter cases relapse and have a fatal termination, have already won an important place for streptomycin in the treatment of tuberculosis in man.

Experience to date also seems to indicate that, in selected types of pulmonary tuberculosis, streptomycin is likely to prove of greatest value, not as a therapeutic entity charged with the "cure" of the disease, but as an important ancillary agent to be employed with discretion and judgment, in combination with other proved

<sup>3</sup> Merek & Co., Rahway, New Jersey; Chas. Pfizer & Co., Brooklyn, New York; Abbott Laboratories, North Chicago, Illinois; Eli Lilly and Company, Indianapolis, Indiana; Parke, Davis & Company, Detroit, Michigan; the Upjohn Co., Kalamazoo, Michigan; E. R. Squibb & Sons, New York.

methods of treatment. It would also seem that the proper timing of its use, particularly in conjunction with pneumothorax and certain major thoracic surgical procedures, and to combat acute, life-threatening episodes such as post-hemoptotic and postoperative lobular and lobar tuberculous pneumonia, will require a type of clinical judgment that comes from an *understanding* of the varied potentialities and complexities of the disease. The optimum timing and best use of streptomycin will not only require objective and careful planning, but also some wisdom in its application. Used otherwise, streptomycin will almost assuredly meet with unwarranted criticism and reverses, if not condemnation.

Present knowledge indicates that streptomycin has certain toxic potentialities, especially with prolonged treatment; that the *place* of streptomycin in tuberculosis is limited, that its usefulness in tuberculosis is limited, and that clinicians should limit its application to those types of tuberculosis for which it is found to be beneficial.

Despite the already demonstrated value of streptomycin in the treatment of certain types of tuberculosis, good sanatorium and hospital care or their equivalent, combined with modern if restrained application of pneumothorax, and the timely use of thoracic surgery, and adequate rehabilitation with competent medical guidance and supervision, are likely to remain the fundamental basis of the management and treatment of tuberculosis for some time to come.

Although one can readily agree with Hart that a substantial part of the bacterial front has been broken as a result of the recent remarkable achievements of chemotherapy of the infectious diseases, nevertheless, nothing resembling a decisive victory of man over microorganisms can be claimed until world control of tuberculosis is attained. This momentous task offers a challenge which will require all of the scientific and humanitarian ingenuity and acumen that man now has or is likely soon to possess.

#### SUMMARY

The history of antibiotic and chemotherapy of tuberculosis is briefly reviewed.

The sulfone compounds, promin, diasone and promizole, proved effective in experimental tuberculosis but much less so in tuberculosis in man.

The first agent with unquestionable beneficial action in clinical tuberculosis is streptomycin. Its efficacy in combination with some of the sulfone compounds is still being investigated.

Streptomycin is decidedly effective in miliary tuberculosis, tuberculous meningitis, ulcerative tuberculosis of larynx and bronchi (and probably intestines), some forms of extrathoracic tuberculosis (particularly in tuberculous fistulae leading to subcutaneous or deep-seated tuberculous foci), and in recent, exudative pulmonary tuberculosis without major cavities and extensive caseation.

Streptomycin is no substitute for bed-rest nor for collapse therapy, but will, in many cases, help such forms of treatment or make them possible.

Streptomycin has certain toxic effects, some of which may be serious. Daily doses of 1.0 g. may be adequate for certain types of pulmonary tuberculosis

and may be decidedly less toxic than daily doses of 2 to 3 g. Toxicity appears more significantly related to total daily dosage than to duration of treatment.

Tubercle bacilli exposed to streptomycin acquire apparently irreversible resistance to streptomycin *in vitro* and in a significant percentage of patients treated with streptomycin.

### SUMARIO

#### *Antibiótico- y Quimioterapia de la Tuberculosis*

Este breve repaso resume la historia de la antibiótico- y quimioterapia de la tuberculosis.

Los compuestos de la sulfona, promina, diasona y promizol, mostráronse eficaces en la tuberculosis experimental, pero mucho menos en la humana.

La primera droga dotada de indudable acción beneficiosa en la tuberculosis clínica es la estreptomicina. Todavía está en investigación su eficacia cuando se combina con algunos de los compuestos de la sulfona.

La estreptomicina es decididamente eficaz en la granulía, la meningitis tuberculosa, la tuberculosis ulcerada de la laringe y los bronquios (y probablemente intestinos), algunas formas de tuberculosis extratorácica (en particular las fístulas tuberculosas que conducen a focos tuberculosos subcutáneos o profundos) y en la tuberculosis pulmonar exudativa reciente sin grandes cavernas ni mayor caseación.

La estreptomicina no constituye un sustituto del reposo en cama ni de la colapsoterapia, pero en muchos casos, sí refuerza esos tratamientos o permite efectuarlos.

La estreptomicina posee ciertos efectos tóxicos, algunos de los cuales pueden resultar graves. Las dosis diarias de 1.0 gm. pueden ser adecuadas para ciertas formas de tuberculosis pulmonar y manifiestamente menos tóxicas que dosis diarias de 2 a 3 gm. La toxicidad parece hallarse netamente más enlazada con la magnitud de las dosis diarias que con la duración total del tratamiento.

Los bacilos tuberculosos expuestos a la estreptomicina adquieren resistencia aparentemente irreversible a la droga *in vitro* así como en un porcentaje significativo de los enfermos tratados con ella.

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# STREPTOMYCIN RESISTANT TUBERCLE BACILLI<sup>1</sup>

Their Development during Streptomycin  
Therapy of Pulmonary Tuberculosis

MYRON W. FISHER<sup>2</sup>

Recent reports (1, 2) indicate that tubercle bacilli are capable of developing resistance to streptomycin, following either *in vitro* or *in vivo* exposure to this antibiotic. Since the therapeutic value of streptomycin for tuberculosis may be greatly influenced by this development of resistance, it was considered important to determine, in a group of patients, the following information: the rate and degree of development of bacterial resistance and the percentage of patients in whom this phenomenon occurs. The present paper is a report of a detailed study of these factors in a group of 20 patients who received 1.8 g. of streptomycin daily for 120 days.

## METHODS

Sputa of the 20 patients were concentrated with sodium hydroxide and cultured on Petraghani's potato-egg medium. These cultures were made of specimens received at weekly intervals before, during and after streptomycin therapy.

The method of testing tuberculostatic agents by depth growth of virulent tubercle bacilli in synthetic liquid media was applied in this study (3, 4). For most of the streptomycin sensitivity determinations, the liquid medium of Dubos and Davis (5) was used. This medium contained 0.05 per cent "Tween 80" (an oleic acid ester) and 0.2 per cent bovine serum albumin; glucose and yeast autolysate were omitted. In addition, organisms obtained after the cessation of streptomycin therapy were tested in the liquid medium described by Youmans (6), which contained 10 per cent human plasma and 2 per cent glycerin as enrichment. The liquid media with various concentrations of streptomycin added were tubed in 2.5 ml. amounts in 15 x 125 mm. screw-cap test tubes. Serial tenfold dilutions of streptomycin were used for the sensitivity determinations, the final concentrations in micrograms per ml. being 1,000, 100, 10, 1 and 0 (control). Suspensions of tubercle bacilli to be tested were prepared by inoculating the entire growth from Petraghani's medium into the Dubos-Davis medium. In this manner, diffuse growth was obtained after eight days of incubation at 37.5° C. These suspensions were standardized turbidimetrically with a Coleman Junior Spectrophotometer against previously determined standards of a known weight-turbidity relationship. The inoculum for each tube in the streptomycin series consisted of approximately 0.01 mg. of tubercle bacilli from the eight day culture. After inoculation, the tests were incubated at 37.5° C. for a maximum of fourteen days, although final readings frequently could be made after seven days. In determining sensitivity, the lowest concentration of streptomycin which completely inhibited growth was regarded as the endpoint.

## RESULTS

*Initial sensitivity:* Tubercle bacilli isolated from the 20 patients prior to therapy were uniformly inhibited by 1 microgram or less streptomycin per ml.

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Indeed, in a much larger series, tubercle bacilli from 110 patients who had never received streptomycin were found to be equally as sensitive. This agrees with the observations of other investigators (2, 6, 7, 8).

*Rate of development of resistance and per cent occurrence:* Streptomycin sensitivity determinations performed on organisms isolated during therapy revealed that tubercle bacilli from 15 of 20 patients, or 75 per cent, remained sensitive to 1 or less mcg. streptomycin per ml. throughout the entire period (120 days) of treatment. Tubercle bacilli from the other 5 patients, or 25 per cent, were streptomycin-sensitive through eleven weeks of treatment, but thereafter began developing varying degrees of streptomycin resistance (see table 1). These determinations were performed in the Dubos-Davis medium.

*Permanence of resistance:* During a six-month period, the 5 streptomycin-resistant strains were frequently subcultured in Dubos-Davis medium and checked for a possible diminution of their degree of streptomycin resistance. No such change was detected. This was also true for the same strains held for six months at room temperature on Petragnani's medium, without subculturing.

TABLE 1

*Development of streptomycin resistance of strains isolated during therapy from 5 patients*

PATIENT NUMBER	WEEK OF STREPTOMYCIN TREATMENT							
	1 through 11	12	13	14	15	16	17	18
9		1*	10	100	1,000	1,000	1,000	1,000
11	All strains sensitive	1	1	1	1	1	10	100
13		1	1	10	10	10	10	10
14		1	10	10	100	100	100	100
16		1	10	10	100	100	100	100

\* Highest concentrations of streptomycin in microgram per ml. which permitted growth.

The permanence of resistance *in vivo* is illustrated by the fact that tubercle bacilli isolated from the 5 patients six months after the end of therapy showed no decrease in the extent of streptomycin resistance. These findings are consistent with other reports (2, 8, 9).

*Comparison of degrees of streptomycin resistance in the Dubos-Davis and the Youmans liquid media:* As noted above, streptomycin resistance occurred in tubercle bacilli isolated from 5 of 20 patients at the end of treatment. This percentage, 25 per cent, was in contrast to the results reported by Youmans *et al.* (1), who found that tubercle bacilli from 8 of 12 streptomycin-treated patients, or 66 per cent, developed resistance. Since the streptomycin sensitivity determinations were performed here in the Dubos-Davis medium, and those in the Youmans report were performed in a medium of different composition (6), it seemed appropriate to compare results using both media. Accordingly, streptomycin sensitivity determinations were done in the two media on the 20 strains of tubercle bacilli isolated at the end of therapy. The results of these determinations are presented in table 2.

Considering tubercle bacilli as streptomycin-resistant if they grew in 10 micrograms or more of streptomycin per ml., it was found that 55 per cent, or 11 of 20 strains, could be called resistant in tests carried out in Youmans' medium. On the other hand, only 25 per cent, or 5 of 20 strains, could be called resistant from tests performed in the Dubos-Davis medium.

The cause of this striking discrepancy was not readily apparent, but some inactivation of streptomycin in the Youmans medium, which contained 10 per cent plasma, seemed a possibility. However, assays performed on both

TABLE 2

*Streptomycin sensitivity in microgram per ml. of 20 strains isolated after 120 days of treatment*

PATIENT AND STRAIN	DUBOS-DAVIS MEDIUM		YOUMANS MEDIUM	
	Growth	Inhibition	Growth	Inhibition
1	1	10	1	10
2	control	1	control	1
3	control	1	control	1
4	control	1	10	100
5	control	1	1	10
6	control	1	control	1
7	1	10	10	100
8	1	10	10	100
9	1,000	*	1,000	*
10	control	1	control	1
11	100	1,000	1,000	*
12	control	1	control	1
13	10	100	1,000	*
14	100	1,000	1,000	*
15	1	10	10	100
16	100	1,000	1,000	*
17	control	1	10	100
18	control	1	control	1
19	1	10	10	100
20	control	1	control	1

\* Minimum inhibitory concentration not determined.

media revealed no measurable decrease of streptomycin potency after fourteen days of incubation, nor was a decrease in potency detected in streptomycin tubes containing actively growing resistant tubercle bacilli. These assays were done according to the procedure outlined by the Food and Drug Administration using the *B. subtilis* filter disk method (10).

#### DISCUSSION

The observation that certain strains of tubercle bacilli become resistant to streptomycin during therapy, whereas others do not, is of great practical importance in guiding the streptomycin therapy of tuberculous patients. It is of particular importance for patients who need additional streptomycin treatment

following an initial course which may have created streptomycin-resistant strains. Youmans and Williston (9) have demonstrated, in experimentally infected mice, that tubercle bacilli resistant to streptomycin *in vitro* are equally resistant *in vivo*, and clinical experience indicates that there is a similar relationship in human cases between the development of streptomycin resistance of the infecting tubercle bacilli and the failure of streptomycin therapy (11).

The results clearly indicate that the choice of a test medium for *in vitro* study of streptomycin as a tuberculostatic agent is of considerable importance, for streptomycin is far more effective against tubercle bacilli in the Dubos-Davis medium than in Youmans' medium. Unless there is universal standardization of the test media used for such study, there will be considerable confusion in interpreting results reported from various laboratories. In the present report, there are 6 strains of tubercle bacilli whose position relative to streptomycin sensitivity remains in doubt. In the Dubos-Davis medium, these strains would be considered as streptomycin-sensitive; in the Youmans medium, they would be classed as streptomycin-resistant. This discrepancy raises the problem as to whether or not a second course of streptomycin would, by prediction, be effective, for it is difficult to be certain whether the patient's organisms are resistant or sensitive. The answer may be obtained from *in vivo* determinations similar to those of Youmans and Williston (9), but such studies, which are comparatively laborious, cannot be applied routinely. A study of the factors affecting *in vitro* determinations might prove to be more practical.

Investigation of the cause of the discrepancies in results obtained in the two media is being carried out in this laboratory and results will be reported in another paper. Empiric observation points to the "Tween 80" as the critical factor, since this substance as a wetting agent may enhance the action of streptomycin.

#### SUMMARY AND CONCLUSIONS

1. Streptomycin sensitivity tests were performed on tubercle bacilli isolated at weekly intervals from 20 streptomycin-treated patients.

2. Tubercle bacilli remained streptomycin-sensitive in 15 patients (75 per cent) throughout the entire period of 120 days of therapy. In the remaining 5 patients (25 per cent), tubercle bacilli were sensitive through eleven weeks of therapy, but thereafter, throughout the remainder of the treatment period, developed varying degrees of streptomycin resistance. These tests were performed in the Dubos-Davis Tween-albumin medium.

3. Streptomycin sensitivity tests were performed in the Dubos-Davis and the Youmans media on 20 strains of tubercle bacilli isolated at the end of therapy. In the Youmans medium, 11 of 20, or 55 per cent, were streptomycin-resistant; in the Dubos-Davis medium, only 5 strains, or 25 per cent, were resistant.

4. The cause of the discrepancy in the results obtained in the two test media is under investigation. Differences in potency of streptomycin were not detected in either medium, for no destruction or inactivation of streptomycin occurred after fourteen days of incubation.

5. Resistance to streptomycin was unchanged in 5 strains after six months, suggesting that streptomycin resistance of tubercle bacilli is a permanently acquired characteristic.

#### SUMARIO Y CONCLUSIONES

##### *Bacilos Tuberculosos Estreptomycinorresistentes*

1. En los bacilos tuberculosos aislados a plazos semanales de 20 enfermos tratados con estreptomicina, ejecutáronse pruebas de la sensibilidad a la estreptomicina.

2. En 15 enfermos (75 por ciento) los bacilos tuberculosos continuaron siendo estreptomicinosensibles durante todo el período de 120 días de terapéutica. En los otros 5 enfermos (25 por ciento) se mostraron sensibles durante 11 semanas de terapéutica, pero a partir de entonces y durante todo el resto del período de tratamiento, manifestaron en mayor o menor grado resistencia a la estreptomicina. Estas pruebas se efectuaron en el medio de albúmina de Dubos-Davis.

3. En 20 cepas de bacilos tuberculosos aislados al final del tratamiento se ejecutaron pruebas de la sensibilidad a la estreptomicina en los medios de Dubos-Davis y de Youmans. En el medio de Youmans, 11 de 20, o sea 55 por ciento, fueron estreptomycinorresistentes, en el de Dubos-Davis, sólo 5, o sea 25 por ciento.

4. Se halla en investigación la causa de la discrepancia en el resultado obtenido en los dos medios. Ni en uno ni en otro medio se descubrieron diferencias en la potencia de la estreptomicina, pues no hubo destrucción o inactivación de la droga tras 14 días de incubación.

5. La resistencia a la estreptomicina permanecía inalterada en 5 cepas al cabo de seis meses, lo cual indica que la estreptomycinorresistencia de los bacilos tuberculosos es una característica adquirida permanente.

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# SENSITIVITY OF TUBERCLE BACILLI TO STREPTOMYCIN<sup>1</sup>

An *in vitro* Study of Some Factors Affecting Results in Various Test Media

MYRON W. FISHER<sup>2</sup>

In a previous report (1) the author indicated the striking discrepancy in results obtained in streptomycin sensitivity tests of tubercle bacilli that were performed in two different liquid synthetic media: the Tween-albumin medium of Dubos and Davis (2) and the plasma-glycerin medium described by Youmans (3). It was found that the Youmans medium permitted growth of tubercle bacilli in much higher concentrations of streptomycin than the Dubos-Davis medium. This paper is a report of a study to determine which ingredients, or combination of ingredients, were responsible for the difference in action of streptomycin in the two test media.

## MATERIALS AND METHODS

As originally used, the two media had the following composition:

### *Dubos-Davis Medium*

Asparagine.....	1.0 g.
Na <sub>2</sub> HPO <sub>4</sub> ·12H <sub>2</sub> O.....	6.3 g.
KH <sub>2</sub> PO <sub>4</sub> .....	1.0 g.
Na <sub>3</sub> citrate·2H <sub>2</sub> O.....	1.5 g.
MgSO <sub>4</sub> ·7H <sub>2</sub> O.....	0.6 g.
Tween 80.....	0.5 g.
Distilled water.....	1,000.0 ml.
(pH was not adjusted)	

After autoclaving the above solution, bovine serum albumin, fraction V (Armour Laboratories), was added to make a final concentration of 0.2 per cent. The serum albumin was made up as a stock 5 per cent solution in 2 per cent sodium chloride. This was heated at 56° C. for thirty minutes and then Berkefeld filtered for sterilization.

### *Youmans Medium*

Asparagine.....	5.0 g.
KH <sub>2</sub> PO <sub>4</sub> .....	5.0 g.
Mg <sub>3</sub> citrate·14H <sub>2</sub> O.....	1.5 g.
K <sub>2</sub> SO <sub>4</sub> .....	0.5 g.
Glycerin.....	20.0 ml.
Distilled water.....	1,000.0 ml.
(Adjusted to pH 7.2 with 40 per cent sodium hydroxide)	

The above solution was autoclaved, and sufficient sterile citrated human plasma was added to a final concentration of 10 per cent.

*Test medium variations:* Preliminary studies indicated that neither *basal* medium (consisting only of asparagine and the various salts) affected the results of streptomycin

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sensitivity determinations. However, for the purpose of this study, the Dubos-Davis basal medium was selected, since this medium without added enrichment was ostensibly a poorer nutrient than the Youmans basal medium. Accordingly, the following eight test media were prepared:

1. Base (Dubos-Davis formula, without Tween or albumin).
2. Base plus 10 per cent plasma.
3. Base plus 0.2 per cent albumin.
4. Base plus 2 per cent glycerin.
5. Base plus 0.05 per cent Tween 80.
6. Base plus 0.05 per cent Tween 80 plus 0.2 per cent albumin.
7. Base plus 2 per cent glycerin plus 10 per cent plasma.
8. Base plus 0.05 per cent Tween 80 plus 10 per cent plasma.

The above media were tubed in 4.5 ml. amounts in 19 x 125 mm. screw-cap test tubes, with 0.5 ml. streptomycin added to make the following concentrations in micrograms per ml.: 1,000, 100, 10, 1, and 0 (control).

*Test strains of tubercle bacilli:* Three strains of tubercle bacilli were selected that originally showed wide variation in results of streptomycin sensitivity determinations performed in the complete Dubos-Davis and Youmans' media. These strains were isolated from streptomycin-treated patients, and they evidenced a high degree of streptomycin resistance in preliminary tests in Youmans' medium. They were isolated from patients following 120 days of treatment with 1.8 g. per day.

These organisms were subcultured in the Dubos-Davis Tween-albumin medium to provide diffuse growth for test inocula in the 8 media previously described. After six days of incubation at 37.5° C., a suspension was obtained containing 0.3 mg. of tubercle bacilli per ml. as measured turbidimetrically (4). The inoculum for each tube in the 8 experimental media consisted of 0.01 mg. tubercle bacilli, or a final concentration of  $2 \times 10^{-3}$  mg. of tubercle bacilli per ml. of medium.

## RESULTS

After inoculation with the test organisms, the various media were incubated for a total of fourteen days at 37.5° C. At the end of this period, readings were made on the basis of the presence or absence of increased turbidity to determine the streptomycin inhibition endpoint. These results are presented in table 1.

## DISCUSSION

The most striking phenomenon evident in this investigation is the enhancement of the action of streptomycin by Tween 80. It is readily apparent that Tween 80, although a growth factor (2), accounted for the difference in results obtained in the Dubos-Davis and the Youmans media in another study (1). As presented in table 1, the basal medium permitted growth of all 3 strains in 1,000 micrograms streptomycin per ml., but the addition of 0.05 per cent Tween 80 to this medium caused complete inhibition of all strains by 1 microgram per ml. of streptomycin. The Tween 80, therefore, was alone responsible for at least a thousandfold increase of the inhibitory power of streptomycin against these 3 strains of tubercle bacilli.

It is also apparent that glycerin, in a concentration of 2 per cent, exerted an effect similar to that of the Tween. The action of Tween or glycerin in this

TABLE 1

*Action of streptomycin on three strains of tubercle bacilli in various media*

STRAIN	MEDIUM	DEGREE OF GROWTH (14 DAYS)				
		Control	mcg. per ml. streptomycin			
			1	10	100	1000
1	Basal medium (B)	+	+	+	+	+
2	Basal medium	+	+	+	+	+
3	Basal medium	+	+	+	+	+
1	B + 0.05 per cent Tween	++++	—	—	—	—
2	B + 0.05 per cent Tween	++++	—	—	—	—
3	B + 0.05 per cent Tween	++++	—	—	—	—
1	B + 2 per cent glycerin	+++	+++	+++	—	—
2	B + 2 per cent glycerin	+++	+++	+++	++	—
3	B + 2 per cent glycerin	+++	+++	+++	—	—
1	B + 2 per cent glycerin + 10 per cent plasma	++++	++++	++++	+++	—
2	B + 2 per cent glycerin + 10 per cent plasma	++++	++++	++++	++++	—
3	B + 2 per cent glycerin + 10 per cent plasma	++++	++++	++++	++	—
1	B + 0.05 per cent Tween + 0.2 per cent albumin	++++	++	—	—	—
2	B + 0.05 per cent Tween + 0.2 per cent albumin	++++	+++	++	—	—
3	B + 0.05 per cent Tween + 0.2 per cent albumin	++++	—	—	—	—
1	B + 0.05 per cent Tween + 10 per cent plasma	++++	++++	++++	—	—
2	B + 0.05 per cent Tween + 10 per cent plasma	++++	++++	++++	++++	—
3	B + 0.05 per cent Tween + 10 per cent plasma	++++	++++	++	—	—
1	B + 10 per cent plasma	++++	++++	++++	++++	++++
2	B + 10 per cent plasma	++++	++++	++++	++++	++++
3	B + 10 per cent plasma	++++	++++	++++	++++	++++
1	B + 0.2 per cent albumin	++	++	++	++	++
2	B + 0.2 per cent albumin	++	++	++	++	++
3	B + 0.2 per cent albumin	++	++	++	++	++

respect cannot be readily explained by their possible toxicity (2), since good growth was obtained in control tubes when these substances alone were added.

Plasma or albumin, in the concentrations used, did not affect the action of

streptomycin, but served to increase the rate and amount of growth to permit clear endpoint readings. However, plasma or albumin appeared to block the effect of Tween or glycerin; but neither plasma nor albumin completely neutralized the action of Tween or glycerin.

It is probable that the potentiation of streptomycin by the Tween, and to a lesser extent by the glycerin, can be explained on the basis of the physical nature of these substances. Tween 80, and probably glycerin, function as surface-active agents. McCulloch (5) points out that "When some substances, which have the property of being surface tension depressants, are added to a bactericidal solution, both the rapidity of penetration and the actual bactericidal efficiency of the bactericide are markedly increased, even though the depressant itself which was added has no toxic action on the test organism. This is probably due to an increase in the rate of diffusion of the bactericide into the bacterial cell, the velocity of diffusion being increased by the reduction of surface tension." Experiments which can demonstrate increased absorption of streptomycin by tubercle bacilli through the presence of Tween, or other wetting agents, will certainly clarify the mechanism of action involved.

These observations indicate that a test medium for determining the action of streptomycin on tubercle bacilli should not contain Tween, glycerin or similar substances. Since such determinations have the immediate purpose of correlation with clinical data in the streptomycin therapy of tuberculosis, it is highly important that the test medium should exclude factors that will give false results. It is also important that the test medium should provide optimum conditions for the earliest detection of streptomycin-resistant tubercle bacilli and the determination of the maximum extent of such resistance. A satisfactory and probably more valid determination may be obtained with a synthetic liquid medium containing only plasma or serum as enrichment.

#### SUMMARY AND CONCLUSIONS

1. An investigation was performed to determine the factors responsible for differences in results obtained in streptomycin sensitivity tests of tubercle bacilli in the Dubos-Davis and the Youmans media.

2. Tween-80 was found to be the critical factor, since this substance alone increased the tuberculostatic power of streptomycin at least one thousand times. Glycerin exerted a similar action, but to a lesser extent.

3. It is recommended that a test medium consist simply of a liquid synthetic base enriched with plasma or serum.

#### SUMARIOS Y CONCLUSIONES

##### *Sensibilidad in vitro de los Bacilos Tuberculosos a la Estreptomicina*

1. En esta investigación se trató de determinar a qué factores se debían los diferentes resultados obtenidos en los medios de Dubos-Davis y de Youmans con respecto a la sensibilidad de los bacilos tuberculosos a la estreptomicina.

2. El "tween-80" resultó ser el factor cardinal, pues esta sustancia por sí sola



acrecentó por lo menos mil veces la potencia tuberculostática de la estreptomicina. La glicerina ejerció una acción semejante, pero en menor grado.

3. Recomiéndase que todo medio de ensayo conste meramente de una base sintética líquida, enriquecida con plasma o suero sanguíneo.

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# TUBERCULOUS MENINGITIS<sup>1</sup>

J. SCHWARZ<sup>2</sup>

In spite of the frequency and importance of tuberculous meningitis, especially in children, relatively few papers have been published recently on pathological findings. Reviewing textbooks and older publications we find many opinions which are not supported by facts. We refer especially to pathogenetic data about infections ascending "through the soft tissue between esophagus, cervical vertebrae, trachea and carotis (Honl)" or about "lymph vessels which accompany the large arteries and whose place of origin may be infected bronchial or mesenteric lymph nodes (Walden)." Neither can we agree with Levinson that tuberculous meningitis can originate in the tonsils.

The authors who regard tuberculous meningitis as hematogenous come closer to reality when they compare this disease with other metastases in miliary dissemination. The work of Kment represents real progress; he proved in well examined cases the nearly constant participation of the chorioid plexus. He supposed that first the plexus is involved and that the infection extends from the plexus to the base of the brain along the periarterial lymph spaces.

A special problem of tuberculous meningitis was studied by Hektoen, namely, the participation of the vessels. He described in detail the changes of the different layers of the vessels. The participation of the intima led him to consider the hematogenous origin of meningitis.

Rich and McCordock are the first to state that the frequent cerebral and meningeal tuberculomata are generally the sources of meningitis. McGregor, McMurray and Schornagel confirm fully the findings of Rich and McCordock; but many other authors who repeated the work of the Baltimore authors were not able to find tuberculomata in such a high percentage, while Radmann and Schwarz agree with the results of Rich. Ragins, Beres and Meltzer disagreed and Beitzke's conclusions are cautious and reserved.

Negative reports are of limited value in biology if some possibility exists, that they are due to technical mistakes. If Rich, McGregor, McMurray and Schornagel can prove tuberculomata as the source of tuberculous meningitis in at least 80 per cent, it is of little interest if other authors find fewer such foci, because this may indicate that they did not use the same technique.

We must call especial attention to the statements of Rich that small (3 mm.) foci in the cerebral cortex near the ventricle or in the leptomeninx are the main causes of meningitis. The fine slicing of the fixed brain is a tiresome and laborious process. The small tuberculomata acquire, with formalin-fixation, a color similar to the surrounding tissue so that they are scarcely visible. This can be shown objectively by the difficulty of presenting them on photographs, even with panchromatic film. The meningeal foci are generally found more easily, because they often appear surrounded by a crown of miliary tubercles and they can be

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found by inspection of the unfixed brain if they lie on the surface. When the meningeal foci are in the depth of a sulcus, they can only be demonstrated by careful cutting.

From the work of Kment, Rich, Korteweg and others, we can clearly see that meningitis cannot simply be compared with other localizations of hematogenous dissemination and that it apparently depends on previously established intracranial secondary foci (that is, after the formation of the primary complex), which, according to Kment, are located in the chorioid plexus, and, according to Rich and others, in the brain substance or in the leptomeninges, as circumscribed tuberculomata.

Now, what is doubtful or disputable:

- (1) Is the most common intracranial localization of the tuberculous focus from which meningitis develops (a) a cerebral or meningeal tuberculoma or (b) a focus in the chorioid plexus?
- (2) How can we explain the great differences in the published data concerning cerebral foci?
- (3) Can a terminal miliary tuberculosis originate from a cerebral tuberculoma?
- (4) Can a deeply located tuberculoma which reaches neither the meninges nor the ventricle cause meningitis?

We shall answer these questions according to the literature and our own experience.

(1) Cerebral tuberculomata and plaque-like meningeal foci are well known since long ago. But Rich and McCordock were the first who emphasized the significance of these tuberculomata in the pathogenesis of meningitis, in opposition to former authors. For instance, Steinmeier claims that conglomerate tuberculomata are very rare and that they still more rarely produce tuberculous meningitis. Kment declares "... the typical so called basal tuberculous meningitis is always connected with a tuberculosis of the chorioid plexus and dependent on it. Conglomerate tubercles are very frequent in tuberculous meningitis during the first year of life, diminishing in more advanced age."

Table 1 gives a survey of the results of different authors. It is necessary to quote these data with a critical mind and with a knowledge of the circumstances under which they were collected. While some of the papers quoted were written before Rich's first publication on meningitis (Kment, Trevelyan, Korteweg, Hartwich, Hektoen), others are based on small numbers (Beitzke, Radmann) and in some papers it is, implicitly or explicitly, stated that not all brains were cut in thin slices (see footnote to table 1). Only the papers by Rich, McGregor, Beres, McMurray, Schornagel, Ragins and this author remain for comparison. Table 1 shows that tuberculomata as possible cause of tuberculous meningitis have been found up to about 90 per cent of cases. With this evidence at hand we may neglect the negative results of other authors. It is easily understood that many tuberculomata escape recognition. We agree entirely with Rich and his followers that meningitis is most commonly caused by cerebral or meningeal tuberculomata, but we believe that they are not the exclusive form of origin.

Kment, from Ghon's Institute, has proved in an excellent study that the chorioid plexus nearly always shows tuberculous changes in cases of meningitis. There is no doubt about this fact and we found it confirmed in all our cases, but these findings can be interpreted in another way than Kment does. Kment thinks that he can recognize the hematogenous origin of tuberculosis of the plexus by the perivascular infiltrates, while in a case in which a tuberculoma discharges its content into the ventricles a different, diffuse infiltration of the chorioid plexus was found. Furthermore, Kment saw that the villi were involved in cases of

TABLE 1

*Cerebral and meningeal tuberculomata in tuberculous meningitis, as reported by 21 authors*

AUTHOR	NUMBER OF CASES WITH MENINGITIS	TUBERCULOMATA		AUTHOR	NUMBER OF CASES WITH MENINGITIS	TUBERCULOMATA	
		Number	Per cent			Number	Per cent
Takahashi.....	105	14	12 (1)	Hartwich.....	113	20	18 (1)
Korteweg.....	123	26	20 (1)	Morice.....	43	12	28 (1)
Saldias.....	28	8	28 (1)	Trevelyan.....	114	33	29 (1)
Radmann.....	10	3	30	Hektoen.....	9	3	33 (1)
Koch.....	15	5	33	Schuermann.....	19	7	37 (1)
Nel.....	61	23	37 (2)	Kment.....	19	7	37 (1)
Ragins.....	39	16	41 (3)	Beitzke.....	14	6	43
Beres.....	28	14	50 (4)	Schwarz.....	42	27	64 (8)
Schornagel.....	34	28	82	McGregor.....	88	78	88 (5)
McMurray.....	11	10	91	Rich.....	82	77	94 (6)
Gsell.....	36	36	(7)				

Note: Some authors do not specify "discharging" and "innocent" tuberculomata.

(1) The brains were not always carefully examined and cut in thin slices.

(2) The author accepts only 12 cases of certain and 3 more of possible origin depending on tuberculomata.

(3) The author accepts only 7 cases of local origin.

(4) Three tuberculomata were not in contact with the surface of the brain and the author considers only 6 cases due to cortical tuberculomata.

(5) Local origin of meningitis was certain in 65 cases and possible in 15 more.

(6) One case arising from direct extension of infection from tuberculous vertebrae.

(7) The author considers only 8 cases of meningitis due to cortical tuberculomata; the paper deals with tuberculoma, and meningitis is discussed only as complication.

(8) Only cases where the fixed brain was cut in thin slices appear in this table.

incipient tuberculosis of the plexus (also without meningitis), while in cases of advanced meningitis the base of the plexus is more involved. We could not confirm these findings (see also Schornagel) and we believe that they would rather contradict the plexogenous origin of meningitis. If in the early cases the villi are affected, this fact would indicate that they are infected from the cerebrospinal fluid which, we believe, happens in fact in the majority of cases. The involvement of the plexus has been studied before and after Kment by Tsiminakis, Soeper, Beres and Huebschmann, but it seems impossible to determine the age of the frequent nonspecific infiltrations in the plexus. In the majority of cases we see only perivascular or diffuse lymphocytic infiltration; formation of

true tubercles with caseation was not often seen. Rich found one among 82 cases, McGregor 4 among 88, Schornagel and I one single case. Small military tubercles are more frequently seen. So we may consider caseous tuberculosis of the choroid plexus an exceptional finding and, therefore, we come to the conclusion that the plexus is, only by chance, the source of infection of the liquor, and that the plexus is generally infected from the cerebrospinal fluid, not excluding the possibility of an occasional blood-stream infection of the plexus, which perhaps explains some cases of tuberculous involvement of the plexus without meningitis.

Appearance and origin of the tubercles of the ependyma may be similar to those in the plexus. The ependymal surface of the ventricles in meningitis is generally covered with small nodules which appear of the same size and form, or a little smaller, as military tubercles. But microscopic examination shows (a fact known for a long time) (Ophüls, Walbaum) that these tubercles are the product of organization of the liquor. On serial sections we can observe bacilli adhering at a certain point, which causes a loss of the epithelial layer with some local reaction, until finally a small typical nodule is formed, occasionally with giant cells but nearly always with tubercle bacilli. So we may suppose that the same or a very similar thing happens to the plexus. For this reason, we believe that the most common intracranial tuberculous foci which produce meningitis are cerebral or meningeal tuberculomata. An involvement of the plexus causing meningeal infection is the exception.

The great difference in the opinion concerning cerebral foci of different authors permits the following explanations: (a) only few workers cut the fixed brain into thin slices; (b) many tuberculomata, which are apparently not related to the surface of the brain or ventricles, are excluded as "innocent," while in reality small connections, invisible to the naked eye, reach the meninges or ventricle and infect them ((figures 1 and 2).

Tubercle bacilli undoubtedly reach the brain by the blood-stream and such a metastasis could take place during any tuberculous dissemination. One could imagine that the tuberculoma itself serves as origin and source of new tuberculous dissemination, exactly as we accept it, for instance in a case of tuberculous osteo-arthritis, salpingitis, etc. In such a way we could also explain the great difference between the age of military tubercles in other organs and the nodules found in the leptomeninges. We could also imagine that further tuberculous dissemination may originate from a cerebral tuberculoma or directly, by rupture into a cerebral vessel, or by way of the perivascular lymph spaces. According to Braus, the lymph spaces of the brain are formed by thin capillary spaces around the blood vessels (Virchow-Robin spaces), which are connected with the subarachnoid space. Hematogenous dissemination from a cerebral tuberculoma could change the reaction of the body and bacilli could settle more easily in the meninges, where they arrive due to the continuous growth of the disseminating or another tuberculoma or in the manner we will discuss later on.

The difference in age between military tubercles in liver, spleen, etc. and those in the meninges would, then, depend on the time when dissemination from the

tuberculoma occurs. This source of dissemination is, of course, rare, but possible. This would explain the apparent absence of disseminating foci in certain cases (see, for example, case 46-V-646).

An apparently deeply situated tuberculoma may undoubtedly reach the surface of the brain or of the ventricle, as we observed repeatedly, especially in the cerebellum. It is impossible to decide macroscopically (especially in the cerebellum and near the cortex of the brain) what kind of relation exists between



FIG. 1

FIG. 2

FIG. 1. Case 39-V368. Apparently deep-seated tuberculoma in the cerebellum. Note meningeal reaction. (43 X)

FIG. 2. Case 39-V368. A few millimeters above the invasion of the subarachnoidal space, the formation of a local productive reaction in the leptomeninx could be demonstrated. (43 X)

meninges and tuberculoma. It is quite possible and even probable that the infection can originate from a deep tuberculoma through perivascular spaces to the subarachnoid space. Practically always we see exudate which seems to penetrate, by way of the perivascular lymph spaces, from the subarachnoidal space into the brain cortex (cortical encephalitis). The fact that lymph circulation may go in either direction (lack of valves in the Virchow-Robin spaces) explains why meningeal infection can originate from a deep tuberculoma through the perivascular lymph spaces. So we may explain satisfactorily the relatively

rare cases in which no cortical tuberculoma nor any other source of meningeal infection can be found.

#### THE AUTHOR'S MATERIAL

Tuberculomata of the cerebral substance vary extremely in size; we have seen some as large as a peach, while others have a diameter of hardly 2 mm. But these small foci are of the greatest importance due to their frequency and their usual cortical localization and because it is so difficult to recognize them. It is frequently necessary to examine the thin slices several times and transilluminate



FIG. 3. Case 48-V-820. Numerous nodules of 2 to 3 mm. size were found in the cortical substance; 32 are due to *Cysticercus cellulosus* and only one (in the centre of the photograph) was a tuberculoma. The cystic formation at the left with the white rice-corn-like mass on the base is a cysticercus with scolex.

them in order to discover some small nodules. We have always examined them microscopically and found that only a part of the suspect foci are really tuberculous, while the greatest number are simulated by uneven fixation of tissue and others are small anemic foci which are quite frequent, particularly in association with tuberculous meningitis (*Erblichungsherde* of Sittig). Also *Cysticercus cellulosus* may be confounded with small cerebral tubercles (case 48-V-820; see also figure 3).

The fixation of the brain requires several weeks; we generally opened the ventricles in order to obtain quicker penetration with formalin. We also recommend to put cottonwool between brain and cerebellum, because otherwise these parts may be found unfixed, even after months. With some experience and patience one can obtain, from the well fixed brain, slices of not more than 2 to

3 mm. thickness. We used a very thin, long, almost flat knife with a double blade, which is superior to the usual brain-knives.

The smallest foci found macroscopically had a diameter of 2 mm. and did not differ much from the surrounding brain tissue, although histologically they showed central caseation. Necrosis is the most striking finding in active cerebral foci. Cell infiltration changes in number and extent; there are generally round cells with one nucleus and, exceptionally, giant cells of the Langhans type. Not



FIG. 4. Case 31-V-15. Caseous tubercle in the central brain substance surrounded by numerous small tubercles and perivascular infiltration (exudative encephalitis). The central nodule may grow by inclusion of the small tubercles; these may be products of perifocal encephalitis or of hematogenous origin like the central focus. (46 X)

always did we find epithelioid cells, and the character of the foci is only recognizable by necrosis, formation of nodules in the periphery and often by the presence of bacilli. Their relation to the adjoining capillaries and small vessels is interesting; it corresponds to a drainage by way of the Virchow-Robin spaces (figure 4). The perifocal exudative encephalitis is important; first, because it contributes to the growth of the foci in centripetal direction and, second, because it facilitates transport of bacilli into the meninges. This provides an excellent explanation for the development of tuberculous meningitis, caused by a deep-seated tuberculoma which does not reach the leptomeninges nor the ventricles. These foci could also, in some cases, be the source of a terminal milky tubercu-



losis, especially if the foci contain many bacilli, as they often do. Where the tuberculomata lie in the cortex without reaching the leptomeninx, we can frequently demonstrate a local reaction which can only be propagated through the Virchow-Robin spaces. We can observe, between these circumscribed, macroscopically quite invisible infiltrations in the leptomeninx, every transition up to the copious exudate of typical tuberculous meningitis.

When the tuberculous foci are situated in the depth of a sulcus, we can clearly notice how the inflammation rises in the subarachnoidal space to the surface of the brain. It is quite striking that there is not always a violent reaction at the point where the tuberculoma reaches the leptomeninx. We have often seen cases where caseous masses break into the subarachnoidal space without violent reaction, even in the presence of numerous acid-fast bacilli. We stress this particularly, because many authors mention, as an argument against the pathogenesis of tuberculous meningitis due to tuberculoma, that there must be many small tubercles at the place of rupture; or they state that, in cases with tuberculomata as the cause of tuberculous meningitis, only some miliary tubercles are seen in the neighborhood of the focus but not typical diffuse meningitis (Huebschmann). Sometimes such tubercles were really found in the leptomeninx around the tuberculomata, especially in cases with meningeal plaques; but often no special local reaction occurs, not even microscopically.

We have seen several cases in which a large tuberculoma remained fixed to the dura, when the brain was removed, leaving the corresponding defect in the brain substance but without visible tubercles in the surrounding leptomeninx, although in these cases the leptomeninx should be expected to have a visible reaction, because in these cases the cerebral tuberculoma perforates the leptomeninx producing an attachment to the dura mater. (These observations are not restricted to old foci with fibrous encapsulation.)

Large tuberculomata have frequently a fibrous wall. No doubt all large foci have once been small ones; but it is doubtful whether they have enlarged *per se* or were formed by confluence of several small nodules, as we often observed. It is probable that both kinds of growth of cerebral foci occur.

Sometimes several foci are found in one brain, apparently caused by the same episode of bacillemia. Some may have a diameter of 2 to 5 mm., while another focus in the same brain may be 1 cm. across. Are these foci of the same age? May the large one be formed by a massive embolus in a small artery, with many bacilli, or does the size only depend on the age of the focus? The generally restricted number of foci seems to indicate that the sporadic and not the massive bacillary disseminations are the main source of cerebral tubercles. It still remains a mystery why the brain substance is attacked so rarely in miliary tuberculosis, and why bacilli should be retained rather during sporadic bacillemiæ, when the number of bacilli in the circulating blood is supposed to be small.

The time during which a tuberculoma can remain in the brain without causing meningitis depends on the localization and size, on the wall of the focus, the number of bacilli, on the reaction of the body, depending on dispositional factors, etc. Tuberculomata of the cortex or near the ventricle may produce relatively

quickly infection of the subarahnoidal space or the ventricle. More deeply seated tuberculomata, especially if they are encapsulated or even calcified (Camerer, Scott), may not cause any symptoms for years or theoretically forever, depending only on their location. Whether or not the number of bacilli is an important factor is not known. In spite of careful examination of the tuberculomata found in the last 19 cases, often by serial sections, it was impossible to find a definite relation between the number of bacilli in the tissue and the condition of the focus. It is nearly impossible to count bacilli in the tissue and the number seen depends, in our opinion, much more on technical details than on the actual number of bacilli. When no or few bacilli are found in an old focus with a fibrous wall (sometimes also in a caseous nodule), this does not prove that few bacilli were present from the beginning; they could have died in the course of time, as it happens in many old foci.

In tuberculous meningitis, appearance, extent and location of the exudate change enormously, but we do not know whether this depends on the age of the focus or the individual, on pathogenesis in the special case, number of bacilli or other factors. There are no systematic studies about the combination of tuberculous meningitis with other bacilli. We observed during a meningococcic epidemic several combined forms. In 2 cases, the exudate appeared purulent, while in one no suspicion existed; but by routine examination, the true character of the infection was discovered. Small and not so frequently larger hemorrhages are found in the brain, in the presence of tuberculous meningitis (figure 5). Twice we found exudate of typical hemorrhagic character. Encephalomalacic destructions are seen, especially in the parts nourished by the *arteria cerebri media*. We found a white encephalomalacia without hemorrhage (Askanazy, Kaup, Nonne, Reuter).

The macroscopic picture and microscopic details of tuberculous meningitis are well described (Sittig, Schornagel, Huebschmann). Special aspects were investigated by Hektoen, Askanazy, Kaup (vascular changes), Kment (chorioid plexus), Ophüls (ependymal lesions) etc. We shall limit ourselves in the following paragraphs to findings which, we believe, are important for the understanding of the pathogenesis and to those which differ from the findings of other authors.

Our 50 cases were all examined microscopically, though only the last 20 were systematically studied. In these, the following organs were examined: hypophysis, *nervus opticus*, *nervus oculomotorius*, *nervus trochlearis*, first and second *nervus spinalis cervicalis*, *ganglion nodosum vagi*, liver, spleen and kidney. From the brain we regularly examined microscopically several parts of the ventricle wall, meninges from the base and the convexity, with corresponding vessels and chorioid plexus. All tuberculomata were studied microscopically, the same as all suspected parts. We could not always make serial sections. But, when certain pathogenetic aspects were to be clarified, we cut complete series; for instance, numerous vessels were examined in order to form our opinion on subendothelial proliferation.

*Hypophysis:* In 21 cases we never found tuberculous involvement; not even in cases where the hypophysis was almost surrounded by tuberculous exudate.

We never observed an involvement of the parenchyma *per continuitatem*. Schmidtman found miliary tubercles only 5 times in 1,200 hypophyses of persons with lethal tuberculosis. We believe that till now little or no attention has been paid to the discrepancy between the incidence of tuberculous involvement of the hypophysis (and epiphysis) and the leptomeninges. We regard this discrepancy as a strong argument against the inclusion of meningitis in the group of simple

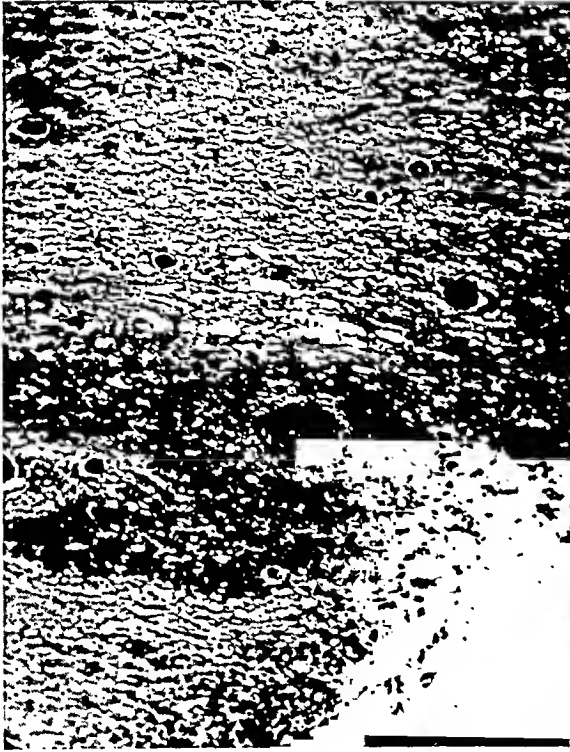


FIG. 5



FIG. 6

FIG. 5. Case 39-V-368. Hemorrhage around a thrombosed vessel; a frequent finding in the cortical zone in tuberculous meningitis. It seems to be a process which appears only a short time before death. (73  $\times$ )

FIG. 6. Case 38-V-312. Peri- and endoneuritis of oculomotorius nerve; we have seen only exceptionally tubercle-like structures, but frequently acid-fast bacilli in the perineural infiltration. (42  $\times$ )

hematogenous metastases, because it would be inexplicable why the hypophysis in miliary tuberculosis should not be infected when the meninges were attacked by the same way. We draw the conclusion that the meninges are not infected directly by the blood-stream, but by the cerebrospinal fluid, which generally is infected from cerebral or meningeal tuberculomata.

*Nerves:* Nineteen times we examined one or both *nervi optici* and always found an intense perineural infiltration, especially impressive in the fibrous wall, characteristic for this nerve, which generally was very edematous. We also exam-

met the *oculomotorius* and *trochlearis* in 19 cases, 10 times the *abducens* and 6 times the *acusticus* and found regularly, on both sides, inflammatory lesions, but we could not discover a direct relation between the quality of the exudate on the base of the brain and the intensity of the peri- and endoneuritis (figure 6). The thickened perineurium has several layers, which are infiltrated by numerous mononuclear cells, mostly lymphocytes. The fibroblasts acquire an epithelioid-like character in many parts, but nodular formations have rarely been observed. Beres also has seen true tubercles in perineural infiltrations. The lesions mentioned can be seen much better in longitudinal than in transverse sections. They occur not only in cranial but also in spinal nerves. (Unfortunately, we did not pay systematic attention to the lower spinal nerves.) Sometimes the perineurium shows necrosis in the vicinity of the meningeal exudate. There are also degenerative lesions in the nerve fibres, especially those adjoining the perineurium. Walther found neuritis in a case of tuberculous meningitis also in the extradural part of some spinal nerves, in disagreement with Appelins and Beres. He believed that the meningeal involvement could be the consequence of an ascending neuritis from a (hypothetical) focus somewhere in the body.

Microscopic study of 12 epiphyses was also negative with exception of one case, where a tuberculous involvement *per continuitatem* was found.

We examined the *ganglion nodosum vagi* 12 times on both sides and 18 times on one side; in no case were exudative lesions found.

With few exceptions, liver, spleen, lung and kidney contained miliary tubercles, as shown in table 2. They frequently differed in size and apparent age from those in the meninges and may have arisen from other disseminations. Among 50 cases of meningitis we found 3 without general miliary tuberculosis.

### *Three Cases of Meningitis without General Miliary Tuberculosis*

*Case 4-207*, a 9-year-old boy with an encapsulated primary focus, had no miliary tubercles but a tuberculosis of the spine with extensive destruction of the atlas and epistropheus. The finding of a tuberculous pachymeningitis at the level of the first and second cervical vertebrae makes it quite probable that the leptomeningitis was the consequence of the destructive bone process.

*In Case 44-V-452*, a 10-year-old girl, we found some miliary tubercles in the tissue surrounding the active primary focus, but these could possibly be of lymphogenous origin. In this case no cerebral tuberculoma was discovered and the pathogenesis of the meningitis cannot be satisfactorily explained. This case has the most intensive vascular lesions we observed. Practically all arteries and veins of the base of the brain have subendothelial proliferations, which frequently cause complete obstruction. The subendothelial proliferation in this case frequently shows nodules with epithelioid and giant cells and does not differ at all from tubercles seen in other organs. It is striking that in this chronic case the meningeal exudate contains numerous polymuclear leucocytes.

*Case 89-V-368*, a girl aged 12. Duration of disease twenty days. Mantoux test (1:1,000) twelve days before death was negative. Autopsy revealed a fibrocaseous primary focus, 3 mm. in diameter, subpleural, in the right upper lobe with fibrous and caseous foci in the

TABLE 2

*Author's material: 50 cases of tuberculous meningitis and 8 cases of tuberculoma without meningitis††*

NUMBER	AGE	SEX	PRIMARY FOCUS	MILIARY TUBERCLES IN				TUBERCULOMA INTRACRANIAL	OTHER HEMATOGENOUS FOCI
				Lung	Liver	Spleen	Kidney		
1-173	18m.	M	?*	+++	+++	+++	+++	†	Thyroid
2-191	7m.	M	Caseous	+++	++	+++	+	Meningeal	
3-197	18m.	F	Caseous	+	+++	+++	—	†	Atlas, epis-tropheus
4-205	9y.	M	Fibrous	—	—	—	—	†	
5-295	9y.	F	Caseous	+	+	+	+	†	
6-315	15m.	F	Caseous	++	++	+++	+	†	
7-385	10y.	M	Caseous	+	+	+++	+	†	
8-442	3y.	F	Caseous	+	+++	+++	—	†	
9-213	10y.	F	Caseous	++	+++	+++	+++	1—cerebral	
10-225	13m.	F	Caseous	—	+	+++	—	No	
11-236	3y.	M	Caseous	++	+++	++	+	1—cerebral	Osteoarthritis
12-237	2y.	F	?*	++	+	+	—	No	
13-241	15m.	F	Caseous	—	++	+	—	1—cerebral	
14-297	3y.	F	Caseous	++	+++	+++	+++	2—cerebral	
15-298	6y.	F	Calcif.	++	++	+++	—	No	
16-304	6y.	F	Caseous	+++	+++	+++	+	5—cerebral	
17-337	12y.	M	Caseous	+	+	++	+	No	Osteoarthritis
18-344	10y.	M	Calcif.	+	+++	+	++	Meningeal	
19-355	7m.	F	Caseous	+++	+++	+++	+	8—cerebral	
20-374	30m.	F	Calcif.	+	++	++	—	2—cerebral	
21-395	15m.	M	Caseous	+	+	+	—	No	
22-400	2y.	M	Caseous	+	+++	+++	—	No	
23-417	9y.	F	Caseous	+	+++	+++	—	No	
24-440	8y.	F	Caseous	++	++	+++	++	No	
25-450	4m.	M	Caseous	+++	+++	+++	++	1—cerebral	
26-451	5y.	M	Caseous	+++	+++	+++	+++	No	
27-457	8y.	M	Caseous	+	++	++	—	No	
28-461	16m.	M	Caseous	+++	+++	+++	+++	12—cerebral	
29-482	10m.	F	Caseous	+	++	++	—	1—cerebral	
30-483	11y.	F	Caseous	+	++	++	+	No	
31-V-45	42y.	M	Calcif.	+++	+++	+++	+++	Meningeal	Prostate
32-V-147	4m.	M	Caseous	+	++	+++	+	No	
33-V-202	12y.	F	Caseous	+++	+++	+++	+++	57—cerebral	Adrenals, thyroid
34-V-210	5m.	M	Caseous	+++	+++	+++	+	No	
35-V-262	73y.	M	?*	+++	++	++	—	2—cerebral	Prostate
36-V-291	10y.	M	Caseous	++	++	++	—	Meningeal	
37-V-305	7y.	F	Caseous	+	+	+	—	No	
38-V-312	20y.	F	Caseous	++	++	++	++	1—cerebral	
39-V-368	12y.	F	Caseous	—	—	—	—	1—cerebral	Genital, bones
40-V-465	6y.	F	Caseous	+++	+++	+++	+++	1—cerebral	

TABLE 2—Continued

NUMBER	AGE	SEX	PRIMARY FOCUS	MILIARY TUBERCLES IN				TUBERCULOMA INTRACRANIAL	OTHER HEMATOGENOUS FOCI
				Lung	Liver	Spleen	Kidney		
41-V-474	3y.	M	?**	?	?	?	?	2—cerebral	?
42-V-432	26y.	M	Calcif.	—	—	—	—	Meningeal	Genital, adrenal
43-V-480	24y.	F	Caseous	++	+	+++	++	Meningeal	Genital
44-V-452	16y.	F	Caseous	+	—	—	—	No	Chorioid plexus
45-V-557	30y.	F	Calcif.	++	+++	+++	+++	5—cerebral	
46-V-646	46y.	F	Calcif.	+++	+	++	+++	17—cerebral	
47-V-667	16y.	F	Caseous	+	+++	+++	+++	12—cerebral	
48-V-820	36y.	F	Calcif.	—	—	—	+	1—cerebral +1—meningeal	
49-V-854	20y.	M	?*	+	+	+	+	Mening. + cerebral	
50-V-889	3y.	F	Caseous	+	++	+	+	1—cerebral	

## Tuberculomata without meningitis

I-174	6y.	F	Fibrous	+	—	—	—	1—cerebral	Ostitis
II-203	20m.	M	Caseous	++	+++	+++	++	1—cerebral	
III-228	14m.	M	Caseous	++	+++	+	+	1—cerebral	
IV-127	20y.	F	Calcif.	+++	+++	+++	+++	1—cerebral	Genital
V-344	3y.	M	Caseous	+++	+++	+++	+++	1—cerebral	Pancreas
VI-610	14y.	M	Calcif.	+	+	++	++	1—cerebral	
VII-621	20y.	F	?*	++	—	—	—	1—cerebral	
VIII-878	28y.	F	Calcif.	+	+++	+++	++	Meningeal	

†† 34 cases of this series are included in a paper published in Rev. Sudam. Morf., 1945, 3, 35.

\*? The Ghon-focus was not found, but tuberculous, intrathoracic lymphadenitis.

\*\*? Only brain-autopsy performed.

‡ Brain was not cut systematically into thin slices.

regional lymph nodes. No tubercles were found in the lungs, liver, spleen and kidney on macroscopic and histological examination. Copious gelatinous exudate was present on the base of the brain and few small tubercles in the Sylvian fissures; the plexus did not show any macroscopic tubercles. *Hydrocephalus internus* with marked dilatation of the lateral ventricles was found. Microscopic study revealed a tuberculoma, 3 mm. in diameter, in the cerebellum, which destroyed the cortex and reached the surface. In the leptomeninges, at the point of contact with the tuberculoma, some productive tubercles and copious exudate were seen. There was a deep-seated tuberculoma of the cerebellum which extended to the surface (figures 1 and 2).

From this case we may learn the following:

- (1) The difficulty to find the discharging focus; the tuberculoma was found almost by accident.
- (2) The necessity of serial sections, in order to recognize the importance and topography of cerebral tubercles.

(3) The presence of single disseminated foci in the brain without tubercles in other organs.

The chorioid plexus is edematous with lymphocytic inflammation. The involvement of the cortex by way of the periarterial lymph spaces is intense. The ventricular ependyma shows numerous foci which are products of organization of the liquor, because the entire ependyma is covered with infected cerebrospinal fluid. Where small ependymal defects exist, little granulomata of round cells are formed (with rare giant cells) (figure 7) and with abundant tubercle bacilli.



FIG. 7. Case 37-V-305. Ependymal tubercle. With magnification 120 the tuberculous structure with giant cells of the Langhans type is obvious; only a few glial fibers but many tubercle bacilli are demonstrable in such formations.

The ependymal lesions had nearly always the same aspect: very small defects of the epithelial layer covered by exudate which accumulated in form of a mushroom (figure 7). These small formations are composed of lymphocytes, fibrin and few glia cells. The capillaries immediately below these lesions are enormously dilated. Many of these capillaries are surrounded by lymphocytes which accumulate with preference on the side nearest to the ventricular surface. Evidently these perivascular infiltrates have been mistaken for independent inflammatory lesions, which caused the division of the ependymal involvement into superficial and deep ones (Ophüls). In our opinion, there is only one lesion—the superficial one; the perivascular infiltration is secondary and comparable

to the perivascular infiltration constantly observed in the cerebral cortex in cases with abundant meningeal exudate. We have repeatedly seen superficial ependymal lesions alone, but never perivascular subependymal infiltrations without a superficial focus. In the neighborhood of the ependymal infiltrations we constantly observed edema under the epithelial layer, resulting even in epithelial desquamation.

Ependymal lesions are described principally by Ophüls, Walbaum and Takahashi; they agree, that the superficial ependymal nodules are products of organization of the infected cerebrospinal fluid; we consider the perivascular subependymal infiltrations as secondary "drainage" through the Virchow-Robin spaces.

The pathology of the chorioid plexus in tuberculous meningitis was systematically studied by Kment. True specific lesions are not found constantly. Our attention was attracted by the enormous dilatation of the vessels of the plexus. Sometimes the vessels were surrounded by lymphocytes and sometimes these perivascular infiltrations could be seen even in the villi. We cannot agree with the observations of Kment about the formation of infiltrates in fresh cases in the villi and in old cases in the base of the chorioid plexus. The plexus is believed to possess functions of secretion, and, according to others, of filtration, but it is not impossible that it has absorbing functions as well. It seems quite possible that sometimes the plexus is attacked by tuberculosis sooner than other parts of the brain, but in this case it must be visible. It does not seem justified that Kment attributes every cellular infiltration to tuberculosis, or that Huebschmann declares that tubercle bacilli are eliminated by the plexus, without causing any local reaction. We do not know whether the plexus and especially the villi can be infected from the liquor; however, it seems probable, especially in analogy to the formation of the ependymal tubercles. We never found such intense alterations in the vessels of the plexus as on the base of the brain. We never observed typical subendothelial proliferation, wall necrosis (especially of the media) or thrombosis.

We consider the tuberculosis of the chorioid plexus and ependyma of no or exceptional importance for the origin of tuberculous meningitis, and we believe that both are frequently the consequence of infection by the cerebrospinal fluid. The incidence of inflammatory reaction in plexus and ependyma is nearly constant in tuberculous meningitis.

(McMurray found neither ependymal nor plexus lesions in 11 cases — an unusual finding, in disagreement with numerous authors and with our experience.)

We wish to describe 3 interesting cases; the first 2 are examples of tuberculoma which may be the origin of final hematogenous dissemination, the third has diagnostic interest.

#### *Two Tuberculomata Which May Be the Origin of Hematogenous Dissemination*

*Case IV-127*, a tuberculoma which does not reach the cerebral surface, located in the right central anterior convolution in the white substance. This case demonstrates that the



infection of the perivascular spaces can extend from a tuberculoma to the surface. There were diffuse caseous processes in the lungs and miliary encapsulated tubercles were found. On macroscopic examination meningitis was not seen, but microscopic examination revealed a discrete but general meningeal fibrosis and an increased number of lymphocytes in the subarachnoidal space. The miliary tubercles in the liver seemed to belong to at least three different phases of hematogenous dissemination. There were very small foci, necrotic without granulomatous tissue and others with epithelioid and giant cells, while the oldest ones were fibrosed. In the adrenals there existed an old caseous process. In the vicinity of the cerebral tuberculoma numerous vessels, both capillaries and larger ones, were surrounded by lymphocytes. This was an infection of the Virchow-Robin spaces and, because such lesions were not found in other cerebral parts but exclusively around the tuberculoma, it is evident that bacilli from the tuberculoma reached the surface of the brain through the perivascular spaces. The possibility exists that they may facilitate the passage of bacilli from the tuberculoma into the blood stream.

This case is of interest because:

- (1) It shows that the absence of visible meningeal alterations is not sufficient to exclude the presence of a pathological process.
- (2) We observe the drainage of inflammatory products from tuberculomata, which do not reach the brain surface, through the Virchow-Robin spaces to the subarachnoidal space.
- (3) The intense perivascular inflammation suggests that, in this case, repeated hematogenous disseminations might possibly have had their origin in the cerebral tuberculoma (compare figures 4, 8, 9 and 10).
- (4) This case illustrates the slow growth of cerebral tuberculomata; therefore we can understand that clinical symptoms of a meningitis regress even in cases where the presence of tubercle bacilli was bacteriologically confirmed. We refer to a case of Blacklock where *intra vitam* bacilli were found in the cerebrospinal fluid and where the autopsy revealed a cerebral tuberculoma without meningitis, and to 3 cases of McGregor, which appeared clinically well years after tubercle bacilli were found in the cerebrospinal fluid. Also Sanhueza has recently published 5 cases of cerebral tuberculoma with favorable outcome.

*Case 46-V-686*, a female, 46 years old. In October, 1945, a cervical lymph node was removed. Twenty days later she had fever, vomiting and nuchal rigidity. The patient died twenty-five days after the extirpation of the cervical lymph node. At postmortem examination 17 tuberculomata were found in the brain, 6 of them in the cerebellum. A Ghon focus was in the left lower lobe and the corresponding lymph node was completely calcified. Numerous miliary tubercles were scattered throughout all pulmonary lobes and in the kidneys, and scanty tubercles were seen in liver and spleen. No active caseous focus was found in the body with the exception of the cerebral foci and the (extirpated) lymph node, which showed a diffuse caseous lymphadenitis. The bronchomediastinal lymph nodes were not involved. The lower tracheobronchial nodes showed tuberculous hyperplasia. Several of the brain tuberculomata reached the meninges and meningeal caseous plaques were also found microscopically. The meningitis originated undoubtedly from one or more of the cerebral or meningeal foci. It is possible that a focus in a tonsil or another oral focus was the source of cervical lymphadenitis, but no focus was found in the oral cavity. The final miliary dissemination originated in one or more of the cerebral



FIG. 8

FIG. 8. Case 31-V-45. Meningeal plaque with intense vascular involvement; note the perivascular infiltration in the cortical zone of the brain near the surface. (46  $\times$ )



FIG. 9

FIG. 9. Case 39-V-368. The perivascular (Virchow-Robin) spaces are filled with lymphocytes (and bacilli); does this infiltration progress always in the direction from the subarachnoid space to the brain, or can the leptomeninges be infected by this way from a deeply located tuberculous focus? (43  $\times$ )



FIG. 10. Case 37-V-305. Small cortical and superficial tubercles, evidently secondary to the meningeal plaque. (42  $\times$ )

tuberculomata or in the caseous lymphadenitis, the only foci found to be older than the final miliary tuberculosis.

### *Cysticercosis Cerebri and Tuberculous Meningitis*

*Case 48-V-820*, a female 33 years old, suddenly fell ill fourteen days before death with general pains, intensive headache and a stiff neck. The cerebrospinal fluid contained 68 leucocytes per cmm. A blood count revealed 11,200 leucocytes and the differential count showed an eosinophilia. Autopsy revealed meningitis with gelatinous exudate over the base of the brain. In the lungs there were old fibrous tuberculous lesions. There were caseous foci in the left kidney with ulcerative, tuberculous cystitis and caseous bilateral salpingitis. In the *cisterna venae magnae Galeni* a *Cysticercus racemosus* of bean size was found. In different parts in the cortical as well as in the medullary substance nodules were found, some of a diameter of 2 to 3 mm., with a yellowish and hard centre (figure 3). We suspected cysticercosis combined with multiple tuberculomata. Microscopic examination revealed that all 33 foci were due to cysticercus with the exception of 2, one of which was a meningeal and the other a cerebral tuberculoma.

Evidently, the combination of tuberculous meningitis and cysticercosis is rare, although the frequency of the first and the relative importance of the second in some countries led us to consider the combination. Asenjo, in Santiago, collected 36 clinical cases of cerebral cysticercosis in a few years.

### INFLUENCE OF SEX, AGE, CLIMATE AND OTHER FACTORS UPON TUBERCULOUS MENINGITIS

Table 3 shows that tuberculous meningitis is fairly evenly distributed between the two sexes. Some authors (Nobécourt, Schelling) claim that sex differences exist in some age groups, but sex distribution of the hospitalized patients is not known.

Everywhere in the Southern and Northern hemisphere, cases of tuberculous meningitis increase during the winter and spring, while in summer and autumn the lowest mortality is noted (table 4). Before looking for the explanation of this fact, we must consider that the general mortality is also subject to seasonal variations (table 5). Therefore, the preference of the cold months is no characteristic of meningitis mortality but a general phenomenon. The lack of vitamins at the end of winter and frequent colds, which weaken the general resistance, may be the factors which cause the seasonal increase. It is conceivable that confinement in houses and poorly ventilated rooms during the winter account for more primary infections, which, after several months, terminate as meningitis; but neither of these factors explains the increase of tuberculous meningitis during the coldest months.

That tuberculous meningitis is more frequent in childhood than in later life has been known for a long time, but the age-specific mortality within childhood is poorly known. Figures based on clinical and postmortem diagnoses differ from those based on vital statistics, as shown in table 6. While the diagnosis of the first group is correct in the great majority of cases, the accuracy of the diagnoses in the second group depends greatly on the percentage of certificates made

by physicians. However, the age distribution in the hospitalized population may not be representative of the total population. Official vital statistics from different countries show large discrepancies (table 7), and there is a marked difference in age distribution between autopsy material and vital statistics (table 8). We must, therefore, conclude that it is quite impossible to state exact figures for the real age distribution of tuberculous meningitis. The same uncertainty applies to the first 12 months. Out of a total of 315 cases which died within the first year (cases reported by Blacklock, Wollstein, Schwarz, Siegel, Saldias and Rich), more than two-thirds died during the second half of the first year. In contrast, the Chilean mortality statistics show an equal distribution of deaths of

TABLE 3  
*Sex distribution of tuberculous meningitis*

AUTHOR	MALES	FEMALES	TOWN OR COUNTRY
Kment.....	434	335	Prague, Czechoslovakia
M'Cracken.....	3,133	2,873	Glasgow, Scotland
Orosz.....	1,316	1,285	Vienna, Austria
Bonaba.....	505	495	Montevideo, Uruguay
"Montivideo".....	1,133	1,094	From Bonaba's paper
Morice.....	194	193	Santiago, Chile
Blacklock.....	124	117	Glasgow, Scotland
Edson.....	1,173	1,196	New Zealand
Schornagel.....	17	17	Rotterdam, Netherlands
Rosenblum.....	53	48	Chicago, U. S. A.
Villa.....	270	222	Rome, Italy
Saldias.....	21	24	Santiago, Chile
Kinnear.....	44	56	England
Schwarz.....	20	28	Santiago and Valdivia, Chile
"Chile" (1936-1942).....	3,172	2,897	
Total.....	11,609	10,880	
Per cent.....	51.5	48.5	

tuberculous meningitis in the first and second half-year. Among 622 cases of tuberculous meningitis which died during the first year (Bonaba, Blacklock, Orosz, Levinson, Siegel), only 10 did so during the first 3 months. Siegel could not find a single case below the age of 2 months among 3,124 cases of tuberculous meningitis which he collected from the literature.

The available evidence suggests strongly that tuberculous meningitis develops most frequently within a few months after primary infection, since a still active primary focus is frequently found in patients who died of tuberculous meningitis.

It seems unlikely that there exists a special susceptibility of the brain and meninges in childhood. The frequency of meningitis in children probably depends simply on the frequency of primary infections. Our opinion is confirmed by the changing age-specific mortality rate, for example, in New Zealand and

TABLE 4

*Distribution of tuberculous meningitis by months in different countries*

	MONTH												TOTAL	COUNTRY, DATE
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII		
Gottzl. ....	476	456	544	586	598	519	520	381	300	313	285	354	5,332	Vienna 1917-26
Levinson .....	55	52	74	71	71	82	68	66	73	54	40	56	762	Chicago 1926-32
Kment* .....	88	70	70	82	76	70	62	63	36	45	40	45	747	Prague 1913-23
Blacklock .....	16	17	26	31	28	33	19	17	15	13	9	17	241	Glasgow 1932-33
Blacklock .....	17	16	19	15	19	27	7	19	3	9	16	13	180	Arpath 1929-39
Simon .....	180	160	220	210	240	190	205	140	145	125	130	150	2,095	Glasgow 1890-1923
Italliday* .....	13	15	88	74	49	9	8	11	7	4	6	6	286	Rome 1903-22
de Villa .....	9	12	17	14	12	8	8	4	7	7	18	9	132	Hamburg 1911-13
Steinmeier .....	7	6	13	4	4	5	4	2	8	8	6	2	69	Paris 1925
Debré .....	4	4	15	11	4	7	8	14	8	8	8	10	101	Chicago 1929-30
Rosenblum* .....														
Total .....	865	808	1,086	1,098	1,101	950	910	719	602	586	558	662	9,945	Northern Hemisphere
Per cent. ....	8.7	8.1	10.9	11	11.1	9.6	9.2	7.2	6	5.9	5.6	6.7	100.0	
Bonaba .....	74	61	74	57	70	73	104	103	97	110	92	85	1,000	Montevideo 1922-42
Morice .....	30	29	21	21	20	47	29	42	41	36	40	31	387	Santiago 1942
Total .....	104	90	95	78	90	120	133	145	138	146	132	116	1,387	Southern Hemisphere
Per cent. ....	7.4	6.5	6.8	5.6	6.5	8.7	9.6	10.5	9.7	10.5	9.6	8.6	100.0	

\* Approximately (from a chart).

Scotland (Edson) with the concurrent shift to older age groups of tuberculous meningitis.

A healed Ghon focus is found only in relatively rare cases of tuberculous meningitis.

We may conclude that tuberculous meningitis in children and in adolescents is distinctly more frequent than in the adult. The second and third half-year shows the greatest absolute number of deaths from tuberculous meningitis.

TABLE 5

*Distribution of all deaths, by months; and of deaths from tuberculous meningitis, by months, Chile, 1941-1945*

	MONTH											
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
Monthly deaths from all causes in per cent of total annual deaths.....	10.5	8.2	7.6	6.8	6.9	7.1	8.1	8.4	8.5	9	8.9	9.8
Monthly deaths from tuberculous meningitis in per cent of annual deaths.....	7.4	6.5	6.8	5.6	6.5	8.7	9.6	10.5	9.7	10.5	9.6	8.6

TABLE 6

*Age-specific deaths from meningitis in childhood, in percentage of all deaths from tuberculous meningitis in childhood*

(Note difference between statistics from autopsy or clinical material and public health reports)

AGE BY YEARS	AUTOPSY MATERIAL*		MORTALITY STATISTICS (CHILE 1936-1944)		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
0- 1	437	16	951	15	1,388	16
1- 3	947	35	1,660	27	2,607	29
3- 5	571	21	929	15	1,500	17
5- 9	511	19	1,624	26	2,135	25
9-14	260	9	971	16	1,231	13
Total . . . .	2,726	100	6,135	99	8,861	100

\* Includes 1,513 cases from Siegel, 995 from Bonaba, 180 from Simon and 38 from the author.

Some differences between the statistics of different countries are also due to the different age distribution of the living population: in Chile, 37 per cent and in the U.S.A. only 25 per cent of all living persons are under 15 years of age (census of 1940 in both countries).

Living conditions are important. Stocks observed in Great Britain that, during the first years of the war, meningitis increased in all age groups. The total tuberculosis mortality increased only 10 per cent for men and 9 per cent

for women, but tuberculous meningitis rose 38 per cent in men and 43 per cent in women. Stocks attributes the increase of tuberculosis mortality in general to the poorer ventilation of bed-rooms due to the blackout, to inappropriate (subterranean) rooms, to massing of people in small rooms, to the lack of food and vitamins. But these factors cannot be the cause of a much greater increase of

TABLE 7  
*Age-specific deaths from tuberculous meningitis in Chile and Scotland*

AGE	CHILE 1936-1944		EDINBURGH 1899-1923*	
	Number	Per cent	Number	Per cent
<i>years</i>				
0-3	2,611	50.6	2,923	77
3-9	2,553	49.5	846	23
Total . . . . .	5,164	100.1	3,769	100

\* From Halliday's paper.

TABLE 8  
*Age-specific deaths from tuberculous meningitis, in different countries*  
(Note difference between autopsy material and death certificate records)

AGE	KLENT	HUEBSCHMANN	KAUFMANN	SIMON	BERES	HARTWICH	MC GREGOR	TOTAL AUTOPSY MATERIAL	PER CENT	CHICAGO*	U. S. A.† 1939-1943	CHILE 1936-1944	TOTAL DEATH CERTIFICATE RECORDS	PER CENT
<i>years</i>														
0-10	309	140	67	27	15	57	97	712	43	527	3562	5120	9209	60
10-20	88	45	36	14	3	28	13	227	14	106	861	1653	2620	17
20-30	142	51	41	14	4	11	6	269	16	108	727	733	1568	10
30-40	118	32	22	3	3	12	4	194	12	80	490	250	820	5.3
40-50	59	33	14	1	3	2	1	113	7	55	414	119	588	3.8
50-60	36	31	9	1	1	1		79	5	18	243	43	304	2
60-70	17		3			2	1	23	1		141		141	1
70-∞	1	33						34	2	5	58	41	104	0.7
Total . . . . .	770	365	192	60	29	113	122	1651		899	6496	7959	15354	

\* Levinson (1926-1932).

† Courtesy of G. J. Drolet, Statistician New York Tuberculosis and Health Assn.

tuberculous meningitis. It is only speculation whether this indicates that a greater number of persons acquired a first infection, which in fatal cases often ended in meningitis. Patients with open lesions were evacuated and many open cases, which normally would have been isolated, did not find beds and disseminated the disease.

Trauma is apparently not of numerical significance for the origin of tuberculous meningitis (Ludtmann, Neff). We must mention that slight but repeated

cerebral traumata are probably more frequent in childhood than in other age groups.

Summarizing these possible pathogenetic factors, none seems of proved importance, but the apparent relation to primary infection and, possibly, malnutrition and poor hygienic conditions.

#### TUBERCULOUS MENINGITIS AND ITS RELATION TO OTHER FORMS OF TUBERCULOSIS

The incidence of tuberculous meningitis depends in the first place on the frequency of primary infection during childhood. The high percentage of menin-

TABLE 9

*Relation between miliary tuberculosis (2,343 cases) and tuberculous meningitis (1,936 cases)*

AUTHOR	MENINGITIS WITH MILIARY TUBERCULOSIS			MILIARY TUBERCULOSIS WITH TUBERCULOUS MENINGITIS		
	Meningitis, number	Miliary tuberculosis, number	Per cent	Miliary tuberculosis, number	Meningitis, number	Per cent
Blacklock.....	241	202	84	258	202	78
Huebschmann.....	365	265	73	265	199	75
Kment.....	781	633*	81	1,342	352	26**
Morice.....	43	32	74	80	68	85
Rich.....	82	64	78	75	64	85
Schwarz.....	48	45	94	72	34	47
Gsell.....	—	—	—	28	17	60
Hartwich.....	—	—	—	200	113	56
Kubo.....	—	—	—	23	16	70
Terplan.....	23	22	96	—	—	—
McGregor.....	84	70	83	—	—	—
Schornagel.....	34	25	73	—	—	—
McMurray.....	11	5	45	—	—	—
Ragins.....	39	31	79	—	—	—
Steinmeier.....	132	59	45	—	—	—
Rosenblum.....	53	46	87	—	—	—

\* Minimal number since in 10 cases only brain-autopsy was permitted.

\*\* 1,027 adults with 19 per cent and 317 children with 49 per cent.

gitis in childhood decreases rapidly to below 1 per cent in adults. Essential disagreements are again found between autopsy material and death certificate records.

Tuberculous meningitis is frequently associated with miliary tuberculosis, which has contributed to the wrong concept, that tuberculous meningitis is one of the numerous metastases of hematogenous dissemination. Among 1,936 cases of meningitis (table 9), 78 per cent had miliary tuberculosis. But only 45 per cent had meningitis out of 2,343 cases of miliary tuberculosis. The latter number greatly depends on the age composition of the material. We may conclude



that miliary tuberculosis is associated with meningitis more frequently during childhood than in older age groups.

It is important to define exactly the relation between miliary tuberculosis and meningitis, and we shall try to do so in the following paragraphs. Tuberculous bacillemia is more frequent than it was previously supposed (Liebermeister, Löwenstein). During the first infection, hematogenous dissemination is particularly frequent (*Frühgeneralisation* of Hübschmann). The first infection has sometimes two simultaneous complications which, however, are not connected in the majority of cases. The first one leads to the formation of foci because of high susceptibility of the tissue; the second originates as a consequence of a focus formed during the early hematogenous dissemination and is, therefore, only indirectly dependent on miliary tuberculosis. The fact that about half of all cases of miliary tuberculosis have no meningitis speaks decidedly against the concept that the meninges are infected during the hematogenous dissemination directly from the blood-stream.

The concept "miliary tuberculosis" is ill-defined, as used by different authors. Generally, the formation of multiple small foci of hematogenous origin would be considered as miliary tuberculosis; but how many organs must be attacked to justify the term? It is of great importance for the development of meningitis whether miliary tuberculosis exists in the pulmonary parenchyma or in the extra-pulmonary organs. The lymphogenous endogenous reinfection of Ghon causes, in many cases, only miliary tubercles in the lung, because the rupture of tubercle bacilli takes place in the venous angle, so that the infected blood is first filtered by the pulmonary capillaries. The matter is quite different in cases where infection of the blood-stream proceeds from an intimal tubercle of the great pulmonary veins or from some small vessels in a caseous lung focus. In our experience the latter can be demonstrated more frequently than an intimal tubercle. The production of cerebral and meningeal foci belongs anatomically probably in the latter form of hematogenous dissemination. We can, then, at least partially explain, by anatomical facts, why meningitis is frequent during childhood and rare in the adult. In the first case, tubercle bacilli arrive from a pulmonary focus or a visible tubercle in a vein (after first infection) and they reach the systemic circulation and localize relatively often in the brain, while in the lymphogenous reinfection of the adult, mainly the lungs are studded with tubercles.

McGregor thinks that sometimes the "invasion of the blood-stream from a focus in any part of the body may occasion an awakening of activity which causes an extension of caseation in preëxistent tuberculous foci." Such a reaction in a meningeal or cortical tuberculoma might cause the discharge of tubercle bacilli into the subarachnoidal space. In this manner, miliary tuberculosis might be simultaneous with the onset of tuberculous meningitis, but in the form of a pace-maker and depending on the presence of a preëxistent meningeal or cortical tuberculoma. More than that, McGregor thinks that meningitis may be the source of miliary tuberculosis. Theoretically it is quite possible that an acute miliary tuberculosis derives from vascular lesions of meningitis, since the latter often lasts about three weeks. We go further and think that the cerebral

and meningeal foci might be the source of blood-stream infection in some cases. We almost never miss, in tuberculous meningitis, perivascular infiltrations in the cortex, thrombosed capillaries and grave vascular changes in the centre and vicinity of cerebral tubercles (figure 11). Therefore, it appears quite possible that these foci are not only the source of meningitis, but that they may also produce miliary tuberculosis before, simultaneously or after the beginning of meningitis. Summarizing, may we say that half of all lethal miliary tuberculosis in children is associated with meningitis; miliary tuberculosis in cases of meningitis



FIG. 11. Case 38-V-312. Proliferation of the subendothelial layer in a vein on the base of the brain; the intact endothelium is clearly visible; giant cells. (76 X)

fluctuates between 70 and 97 per cent. The great differences in the age of cerebral foci compared to those in other organs, the occasional absence of miliary tubercles in other organs and the frequent absence of meningitis in cases of extensive miliary tuberculosis plead against a direct causal connection between the two processes. Furthermore, miliary tuberculosis can be secondary to and take its origin from meningitis (McGregor) or even from a cerebral or meningeal tuberculoma (Schwarz), naturally only in cases in which the disseminated tubercles are younger than the cerebral foci, which is practically the rule in cases with cerebral tubercles.

## STATISTICAL DATA CONCERNING CEREBRAL TUBERCULOMATA

Table 10 shows the age distribution of cerebral tuberculomata, which is similar to that of tuberculous meningitis—a very suggestive fact. During the first ten years of life more tuberculomata of the brain are found than during the rest of life.

TABLE 10  
*Distribution by year of cerebral tuberculomata, by age groups*

AGE	SCOTT	AGE	RICH	SCHWARZ	KMENT	GSELL	HARTWICH
0-4	159		43	13		10	
5-9	162		5	3	65	2	15
10-14	67		2	5		4	
15-19	47		2	1	12		1
20-24	49	20-30	1	3	19	23	2
25-34	77	30-40	2	1	10		1
35-44	62	40-50	1	1	7	13	
45-54	20	50-60	1		4		1
55-64	5	60-70				6	
65-74	1						
Total . . .	464		57	27	117	58	20

TABLE 11  
*Number of cerebral tuberculomata in single brains*

AUTHOR	NUMBER OF TUBERCULOMATA						TOTAL
	1	1-5	5-10	10-20	"Many"	More than 1	
Scott . . .	475	171	8	3	71	253	728
Schornagel .	5	9	2	5	3	19	24
Gsell . . .	27	16			14	30	57
Ragins . . .	6					13	19
Beres . . .	4	3				6	10
McGregor . .	12					30	42
Zappert . . .	27					35	62
Schwarz . . .	12	8	3	3	1	15	27
Total . . .	568					401	969
Per cent . .	58.6					41.4	

Table 11 shows that 58 per cent of all cerebral foci are multiple. McGregor describes a case with 130, Beres with 110, Schornagel with 99, Radmann with 64 and, finally, we observed one with 57. The foci in the same brain are frequently of quite different sizes, and it remains doubtful whether all are the result of the same dissemination, and whether their sizes depend only on their ages. In spite of the small volume of the cerebellum, about 33 per cent of all tuberculomata are

found in the cerebellum (table 12). In the cerebrum, the frontal and occipital lobes are most frequently involved (table 13).

Much of the material on cerebral tuberculomata is based upon the survey by Scott and Graves. These authors collected a large number of cases, but this material was published by the respective authors for different reasons: some because of unusual localization, others to demonstrate the differential diagnosis with tumors, and others as a result of systematic studies about meningitis.

TABLE 12  
*Anatomical distribution of cerebral tuberculomata*

AUTHOR	CEREBRUM	CEREBELLUM	PONS	MEDULLA	TOTAL
McGregor.....	349	96	9	5	459
Scott*.....	418	421	120	40	1,002
Schornagel.....	93	14	3		110
Gsell.....	38	27	16	1	82
Schwarz.....	90	39	3		132
Total.....	988	600	151	46	1,785
Per cent.....	55	33			

\* Approximately (from a chart).

TABLE 13  
*Anatomical distribution of cerebral tuberculomata according to lobes*

AUTHOR	FRONTAL	PARIETAL	OCCIPITAL	TEMPORAL	CENTRAL	BASILAR GANGLIA	TOTAL
McGregor.....	106	101	84	25	19	14	349
Scott.....	78	28	60	22	70	134	392
Schornagel.....	25	41	64	16	1	6	153
Schwarz.....	36	9	13	6	4	1	69
Total.....	245	179	221	69	94	155	963
Per cent.....	25.6	18.6	23	7	10	15.8	100.0

Therefore, it is obvious that all statements about age distribution, location, etc. ought to be used with great caution. Among the 815 tuberculomata collected by Scott and Graves, only 13 showed calcification. Camerer added some new cases. Calcification is rare and has no prognostic significance. According to our experience, tuberculomata with fibrous encapsulation may become active. Nodules may develop outside or inside of the fibrous capsule. We do not know whether, just as in lung and lymph nodes, tubercle bacilli may remain alive for long periods in tuberculomata which are calcified and have a fibrous capsule.

## COMMENT

The frequency of meningitis during childhood is closely connected with the incidence of first infection at this age; consequently, we should expect in the future a postponement of the incidence of meningitis in those countries where first infection takes place in higher age groups (U.S.A., New Zealand, Scandinavia).

Most German authors still state that meningitis generally depends on a "primary" tuberculosis of the chorioid plexus, considering the cerebral tuberculoma a rare exception as the source of meningeal infection (only Beitzke and Radmann accept, with reserve, Rich's concept). In other countries, the cerebral and meningeal tuberculoma is accepted as the most frequent source of tuberculous meningitis.

We believe that every objective student of tuberculous meningitis can find that tuberculomata are quite frequent and that, in the majority of cases, these foci are the source of meningeal infection.

Numerous specimens have shown us that apparently deep-seated tuberculomata can reach the brain surface or the ventricles or that, due to the drainage through the periarterial lymph spaces, infection may extend to the meninges. We believe also that caseous tuberculomata may occasionally be the source of a hematogenous dissemination if the bacilli find their way into the lumen of a vessel, which can happen in the tuberculomata of the brain as frequently as in any tuberculous focus in the body.

The alterations of the chorioid plexus, ependyma and cranial nerves are constant in our material, but evidently secondary. Convincing cases of tuberculosis of the plexus as a source of meningitis are exceptional.

In any given case it will be difficult to prove the origin of meningitis, if no discharging tuberculoma is found; but, in our opinion, cerebral and meningeal tuberculomata in visible contact with the surface of the brain certainly prove that they are related to the production of meningitis. The same is true when the rupture of caseous masses into the subarachnoidal space (or ventricle) can be proved only by microscopic study, and even if the local reaction is slight.

The inflammation at the point where a tuberculoma reaches the surface of the brain is not always marked; sometimes a diffuse or circumscribed cascation is found; in other cases small tubercles are present and, finally, in some cases hardly any reaction is visible, but only some thickening of the meninges with pleocytosis (almost exclusively mononuclear); involvement of the vascular walls is present in such cases. The form of reaction depends largely on the topographic location of the tuberculoma. On the base of the brain or cerebellum exudation is generally much more pronounced than on the convexity.

We regard it as a great mistake to doubt the etiological significance of a tuberculoma, because the local reaction is sometimes slight in the vicinity of the focus. Stains for tubercle bacilli generally reveal numerous bacilli at the discharging point, which may be conveyed by the cerebrospinal fluid to places where they find optimal conditions for multiplication. We do not know (and we do not

consider that it is proved) whether very numerous bacilli are necessary to produce meningitis, as Rich supposes.

Just as in meningococcic meningitis (Schwarz), we could often find cellular infiltration of the meninges where the naked eye could not see any pathological changes; therefore, we conclude that the lack of visible exudate does not suffice to exclude the presence of a microscopic inflammatory reaction.

Immunological factors may be responsible for the frequency of tuberculous meningitis shortly after first infection; but meningitis also occurs in the presence of calcified Ghon foci.

#### SUMMARY

Tuberculous meningitis is usually caused by infection of the subarachnoidal space or the ventricles by cerebral or meningeal tuberculomata.

Direct infection of the meninges from the blood-stream, tubercles in the dura or discharging foci in the chorioid plexus seem to be rare sources of tuberculous meningitis; osteomyelitic foci of the skull or vertebrae and trauma are still less frequent causes.

Cerebral and meningeal tuberculomata may also be responsible for hematogenous dissemination, just like any other caseous focus in the body.

Meningitis itself might sometimes be the source of final miliary spread, considering the intense involvement of the meningeal veins.

Deep-seated tuberculomata, which do not reach the surface of the brain, might be responsible for meningitis due to drainage through the perivascular (Virchow-Robin) lymph spaces.

Cerebral tuberculomata are found in cases without meningitis. Similarly, but rarely, meningeal tuberculomata occur without causing meningitis.

Tuberculous meningitis develops, as a rule, a short time after the first infection; this is the principal reason why the majority of cases of meningitis are observed in childhood.

In most cases of meningitis, miliary tuberculosis is also found, whereas miliary tuberculosis occurs in combination with meningitis, especially in children, while adults with hematogenous dissemination rarely die of meningitis.

Vascular alterations are most intense on the base of the brain. We observed panarteritis with and without necrosis and different grades of thrombosis, sub-endothelial proliferation and true tubercles. Veins are similarly involved.

The localization of the exudate on the base of the brain depends directly on pathogenesis and mechanical factors. The majority of cases originate through infection by cerebrospinal fluid from cerebral or meningeal tuberculomata, and the greatest quantity of exudate concentrates where most liquor normally accumulates, that is, in the basal cisternae.

Brain and spinal nerves are almost always involved in the inflammatory process, but apparently secondarily.

The highest incidence of meningitis is in winter and spring and coincides largely with the highest mortality from all causes during these months.

## SUMARIO

La meningitis tuberculosa es generalmente causada por la infección del espacio subaracnoidal de parte de un tuberculoma encefálico o meníngeo.

La infección directa de las meninges por vía hemática, como consecuencia de una tuberculosis de la duramater o de focos tuberculosos de los plexos coroideos parecen accidentes poco frecuentes; osteomielitis del cráneo o de las vértebras y traumatismo son todavía causas más remotas de la meningitis tuberculosa.

El tuberculoma encefálico o (y) meníngeo puede ser responsable -fuera de la producción de la meningitis- de la diseminación hematógena, igual que cualquier foco caseoso en otros órganos.

También la meningitis a veces puede constituir el punto de partida de la diseminación final, tomando en cuenta la intensa participación de las venas meníngeas.

Tuberculomas con localización profunda, que no alcanzan la superficie cerebral, pueden ser causantes de la meningitis através del drenaje por las vainas perivasculares de Virchow-Robin.

Tuberculomas encefálicos se encontraron con cierta frecuencia también en casos sin meningitis; igualmente a veces pueden observarse tuberculomas meníngeos sin meningitis difusa y macroscopicamente visible.

Generalmente la meningitis se produce corto tiempo después de la primoinfección y esto constituye la principal razón para la frecuencia de la meningitis en la infancia; con la postergación de la primoinfección la meningitis va aparecer en edades más avanzadas.

En la mayoría de los casos de meningitis se comprueba una granulía, pero únicamente en niños las granulias se combinan con frecuencia con meningitis; en el adulto solamente una pequeña parte de las diseminaciones hematógenas muere de meningitis.

Los tubérculos endimales constituyen focos organizados de líquido cefaloraquídeo infectado. Su importancia y patología es comparable a las lesiones de los plexos.

Las alteraciones vasculares se observan especialmente en la base del cerebro, donde también son más intensos, que en otra parte. Hemos visto panarteritis con y sin necrosis y trombosis, proliferación subendotelial y tubérculos de la íntima; lesiones parecidas se observan también en las venas.

La localización del exudado depende en primer lugar de la patogenia; como la mayoría de los casos se produce a consecuencia de la infección del líquido cefaloraquídeo debido a un tuberculoma encefálico o meníngeo, el exudado se encuentra en los lugares donde normalmente se acumula más líquido: en las cisternas basales.

Los nervios cerebrales y espinales participan con gran regularidad en el proceso inflamatorio pero evidentemente como complicación.

La prevalencia de fallecimientos por meningitis tuberculosa en invierno y primavera se observa en todo el mundo, pero coincide en gran parte con el aumento de la mortalidad general en estos meses; aparentemente no existen diferencias entre los sexos en cuanto a frecuencia.

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# SEMINAR ON BCG<sup>1</sup>

## INTRODUCTORY REMARKS

HENRY C. SWEANY,<sup>2</sup> MODERATOR

It has been twenty years since Calmette published his first complete monograph on BCG and even at this date there is not complete agreement regarding the exact place of this vaccine in antituberculosis work. Many millions of tests have been made during the last twenty years, but most of them have not been controlled. Of recent years, however, several controlled experiments have been undertaken and we shall this morning be privileged to hear some of these reports. Certain facts have been learned: It has been proved beyond doubt that BCG is harmless, that it is feasible to administer the vaccine to human beings, and that it offers some degree of protection against a later infection with virulent tubercle bacilli.

The unfavorable features are the dangers of contamination or mixing cultures with virulent strains, the difficulty of applying it to great masses of people, the false security that may be engendered by its use, and that it does not afford the complete protection that smallpox vaccination does.

This morning we are to hear from some of the most reliable authorities in the world for and against the value of BCG, and it is hoped that out of this conference there will be crystallized a program of lasting benefit.

<sup>1</sup> Presented before the Medical Section at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 19, 1947.

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## BCG VACCINATION AMONG AMERICAN INDIANS

JOSEPH D. ARONSON<sup>1</sup>

The results obtained under experimental conditions in animals, and the results obtained under controlled conditions in humans by Park and Kereszturi in New York, and by Aronson and Dannenberg in Philadelphia, indicated that a certain degree of protection against tuberculosis resulted from the administration of BCG vaccine.

To evaluate further the effectiveness of this vaccine in the control of tuberculosis and to determine the duration of the tuberculin allergy resulting from this vaccination, a joint study was instituted in 1935 by the Health Division, Office of Indian Affairs, and by the Henry Phipps Institute, University of Pennsylvania. The plan of the study consisted in testing with 0.000,02 and 0.005 mg. of PPD tuberculin all of the school children and as many as possible of the preschool children and adults on certain Indian reservations in the United States and Southeastern Alaska. Those who failed to react to both doses of tuberculin were divided according to age and sex into two groups of approximately equal numbers. One group of these tuberculin-negative persons received an intracutaneous injection of either 0.1 or 0.15 mg. of freshly prepared BCG vaccine suspended in physiological salt solution, while the other group received an injection of physiological salt solution only and served as controls. Neither group was isolated following injection and no changes were made in the habits or mode of living. The site of the intracutaneous injection was examined forty-eight hours later to observe the character of the local inflammatory reaction and to note whether or not a Koch phenomenon had occurred.

In practically every instance where vaccine from a rapidly growing culture had been used, a small ulcer was subsequently noted at the site of the vaccination. These ulcers were followed by superficial scars ranging in size from 5 to 10 mm. in diameter, which have persisted for a period of eleven years and which resemble the scars resulting from vaccinia inoculation. In no instance was surgical intervention necessary for the treatment of these ulcers and in no instance did the regional lymph nodes ulcerate.

Reëxamination of the BCG vaccinated and control cases was made at approximately yearly intervals. Both groups were retested with 0.000,02 mg. of PPD tuberculin and those who failed to react were retested with 0.005 mg. of PPD. At the same time roentgenograms of the chests were made. The tuberculin reactions were read by trained personnel and for the most part by the same personnel for all the annual examinations. The films were interpreted by a roentgenologist who had no knowledge of the tuberculin reaction or whether or not the films were of vaccinated or control cases.

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The population of the Indian reservations offers a unique opportunity to study the effectiveness of control measures in tuberculosis. The morbidity and mortality from tuberculosis are high. Incomes are almost universally low in the areas studied, living conditions poor and homes crowded. These people are of relatively pure stock racially and may be observed over a long period of time with relative ease.

This study was carried out on the Pima Agency, Arizona; the Wind River Agency, Wyoming; the Turtle Mountain Agency, North Dakota; the Rosebud Agency, South Dakota; and in the villages of Southeastern Alaska. The degree of tuberculous infection and disease existing in these areas may be gauged by the

TABLE 1

*Number of deaths from all causes and from tuberculosis in BCG vaccinated and control cases*

GROUP	1936 SERIES				1937-1938 SERIES				TOTAL			
	Num- ber	Num- ber deaths all causes	Num- ber deaths tuber- culous	Num- ber deaths non- tuber- culous	Num- ber	Num- ber deaths all causes	Num- ber deaths tuber- culous	Num- ber deaths non- tuber- culous	Num- ber	Num- ber deaths all causes	Num- ber deaths tuber- culous	Num- ber deaths non- tuber- culous
Vaccinated.....	657	26	2	24	893	29	4	25	1,550	55	6	49
Control.....	616	52	20	32	841	56	32	24	1,457	108	52	56
NEW-BORNS 1939-1941												
	Num- ber	Num- ber deaths all causes	Num- ber deaths tuber- culous	Num- ber deaths non- tuber- culous								
Vaccinated.....	123	7	0	7								
Control.....	139	15	4	11								

fact that only 35 persons ranging in age from 17 to 20 years, who were tested, failed to react to tuberculin and 60 per cent of those who reacted to 0.000,02 mg. PPD tuberculin gave a reaction exceeding 20 mm. in diameter (3+). Roentgenological examination of statistically significant samples of the general population indicated that from 3 to 6 per cent had significant pulmonary lesions of tuberculosis.

At this time there is available the number of deaths from tuberculous and non-tuberculous causes for the total period of observation, as well as the results of the tuberculin tests for the current reëxamination, 1946-1947.

In addition to the original groups, ranging in age from one to 19 years, a supplemental study was initiated during 1939-1941 at two of the reservations. Alternate new-born babies were vaccinated within a few days of birth and those not vaccinated were used as controls. Because of the differences in the length of observation of the different groups, the results are presented separately for each group in table 1.

In order to determine precisely the cause of death in each case the ideal procedure would be a complete and careful autopsy. This was possible in only a few cases. In the vast majority of instances the diagnosis of tuberculosis was based on clinical data, serial X-ray films, sputum examination and examination both cytological and bacteriological of the spinal fluid in cases presenting clinical signs of meningitis.

The most definite and striking comparison between the BCG and control groups is the total number of deaths occurring in each group. Among those vaccinated during 1936-1938 there was a total of 55 deaths, while among the controls of that group there was a total of 108 deaths for the same period. Among the group of new-borns of 1939-1941, there were 7 deaths among the vaccinated and 15 among the controls. Of the vaccinated cases of the 1936-1938 series who died

TABLE 2

*Incidence of tuberculin reaction, 1946-1947, in BCG vaccinated and control groups*

GROUP	VACCINATED 1936					VACCINATED 1937				
	Number	Per cent retested	Per cent positive 0.000,01 mg. PPD	Per cent positive 0.002,5 mg. PPD	Total positive PPD	Number	Per cent retested	Per cent positive 0.000,01 mg. PPD	Per cent positive 0.002,5 mg. PPD	Per cent positive PPD
Vaccinated.....	657	72	64	27	91	893	75	75	17	92
Control.....	616	69	34	5	39	841	73	49	5	54
	NEWBORNS 1939-1941									
	Number	Per cent retested	Per cent positive 0.000,01 mg. PPD	Per cent positive 0.002,5 mg. PPD	Total positive PPD					
Vaccinated.....	123	82	38	43	81					
Control.....	139	81	19	8	27					

from tuberculosis, 2 had a Koch phenomenon following vaccination, indicating that the children were vaccinated during the pre-allergic period of a spontaneous tuberculous infection. One child died approximately six weeks after vaccination from miliary tuberculosis; the second died after nine years also from miliary tuberculosis. In a third case the child who died had had a negative tuberculin reaction one year after vaccination.

Without implying that allergy and immunity necessarily coexist, we have accepted the development of allergy, indicated by a positive tuberculin reaction, as evidence of immunity. We have also employed the tuberculin reaction as an index of the occurrence of tuberculous infection among the unvaccinated groups. The results of the most recent tuberculin tests, using 0.000,01 and 0.002,5 mg. of tuberculin PPD are presented in table 2.

It is evident that a significantly higher percentage of those who received BCG vaccine reacted to tuberculin than of the unvaccinated controls. That a certain

percentage of the tuberculin reactions among the vaccinated may be due to a superimposed infection with virulent tubercle bacilli cannot be denied. The difference, however, in the percentage of reactors in the two groups is so marked that it must be attributed to the allergy induced by the BCG vaccine, administered to the original group eleven years previously.

It has long been recognized that sensitivity to tuberculin, both quantitative and qualitative, is mediated by the dosage and virulence of the tubercle bacillus. Additional evidence supporting this view is indicated by the fact that among the unvaccinated control group a significantly higher percentage react to 0.000,01 mg. tuberculin PPD than among the vaccinated group:

#### SUMMARY

1. Among 1,550 persons, ranging in age from under one to 20 years, who were vaccinated in the period of 1936-1938 with BCG vaccine, 55 have died; 6 of these deaths were due to tuberculosis. Among 1,457 persons of comparable age, who were not vaccinated, 108 have died; 52 of these deaths were from tuberculosis. In a group of 123 children vaccinated several days after birth, 7 have died, but none from tuberculosis. Of 139 unvaccinated new-born controls there have been 15 deaths, 4 of which have been due to tuberculosis.

2. The tuberculin reaction has remained positive in 91 per cent of the cases originally vaccinated in 1936, eleven years after vaccination, while among the control group who were negative to tuberculin PPD in 1936, 39 per cent are now positive.

## THE POSSIBLE USE OF THE VACCINE BCG IN SAN FRANCISCO

J. C. GEIGER<sup>1</sup>

Much is known about tuberculosis but the disease still presents problems of control. Though the tuberculosis seed in the human soil affects only about one per cent of the population, it is very difficult to inculcate in the sufferers from tuberculosis the knowledge of the symptoms that should bring them early to a doctor, and likewise for the doctor to recognize their importance and make an early diagnosis. There is no doubt that tuberculosis in its early stage is one of the hardest diseases to diagnose. It is in this group of early cases on which our efforts must be concentrated.

Another fact is that, of perhaps 60 per cent of the persons infected with the tubercle bacillus, only a minute proportion develop the disease. Therefore, in an overwhelming majority of people there must be great resistance to this infection. The small number, however, who develop the disease presents persons who are the natural soil for the infection. It is this group which must be diagnosed early and, if they have families, these families must be followed in order that the disease be reduced within the family and in the community. It is logical then to send the infected case to a sanatorium and everything possible must be done to keep the uninfected members of the family free of infection. This is particularly true of children. It is also true that this is a costly public health procedure, but the community must pay for its freedom from tuberculosis.

It was in 1882 that Koch discovered the tubercle bacillus. One of the most important developments was the X-ray discovered in 1895. In 1890 the pulmonary tuberculosis death rate in San Francisco was 326.9 and to-day it is 42.2. The basic pattern for the control of tuberculosis in the future could be considered expansion of all public health services and adequate hospital and outpatient facilities, perhaps some type of invalidism insurance for tuberculous families may be possible, and prevention by vaccination. Most of these public health services are presented to San Francisco citizens, with the exception of BCG immunization. The tuberculosis rate in certain areas like Chinatown (122) compared with the rate for the city as a whole (42.2) presents such a problem of prevention, especially of contact to open cases by children.

To evaluate BCG immunization is quite difficult. The results of Calmette and Guérin in Paris, who first began to develop BCG, a bovine strain, in 1908, were first published in 1920 and appeared at the time to reveal irrefutable evidence of the vaccine's effectiveness. BCG is a culture and is prepared in various ways, the more recent being a Russian method (Public Health Reports, February 7, 1947) in which a small amount of culture is mixed with glucose and dried. The essential features are that the strain be a pure culture of the proper and right strain and that it be viable. These authors formulated their rationale of prevention by stating that the virulence of bovine tubercle bacilli is first reduced

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by special culture procedures, then the vaccine so processed is introduced intracutaneously in infants and children who are in contact with cases ("shedders") of the disease or of the bacillus. Such introduction of the attenuated organism may initiate a mild self-limiting process which may produce resistance against virulent strains of both bovine and human tubercle bacilli.

Those opposed to BCG immunization emphasize that the imposition of infection, no matter how mild or how much resistance to virulent organisms it may produce, is a doubtful procedure in American life except perhaps where the incidence or degree of exposure is much greater than that which obtains in the country as a whole.

The publications of Holm of Denmark and Hertzberg in Norway show this type of prevention to be very desirable. Levine and Sackett in New York City have two diametrically opposed reports and therefore one must assume from these statistics a rather conservative attitude.

Further experience in this country was at the Tice Laboratory of the Chicago Municipal Tuberculosis Sanitarium and the University of Illinois College of Medicine. The conclusion from their results was that it is of definite value in the prevention of tuberculosis, especially in the early years of life.

The work of Aronson and Palmer among American Indians indicates that BCG vaccination is associated with a marked protection against the development of tuberculosis. These authors used unvaccinated persons as control groups.

It may be of interest to know that a number of years ago a committee of the University of California, Drs. Shipman, Pope, Meyer and Geiger, recommended that for medical students BCG vaccine should be used on a volunteer basis, and, according to Doctor Meyer, is to be reinstituted at the University of California this fall.

The source and preparation of BCG vaccine naturally is of extreme importance. At this moment it is not being prepared commercially. Apparently these are the sources of certified BCG vaccine: the United States Public Health Service, the Tice Laboratory of Chicago Municipal Tuberculosis Sanitarium, the University of Illinois College of Medicine, and the Henry Phipps Institute of Philadelphia.

In San Francisco, for several years, annual reports have been made on cases of tuberculosis found by tuberculin testing in school children. In 1941, the first year of this report, 28 per cent of the cases found were in Chinese children. In 1946, only 19 per cent of the cases found were Chinese. Some of this decline may be partially accounted for by the fact that through the war years there was little growth in the Chinese population, but it does not minimize nor detract from the value and effectiveness of tuberculin testing.

A check on actual tests done in the schools on Chinese enrolment shows that, for the fiscal year 1939-1940, 27 per cent of the tests revealed reactors. For the fiscal year 1945-1946, this had been reduced to 5 per cent.

As a result of testing in the 1939-1940 period a total of 18 cases in the Chinese group was found and hospitalized. Twelve others were recommended for home care. In the 1945-1946 period only 2 cases were found and hospitalized and one brought under home care.



In the studies of new cases reported to the Bureau of Communicable Diseases on age distribution, it is found for 1943 that 24 per cent of the Chinese cases were in the school and preschool groups; in 1944, 22 per cent; in 1945, 20 per cent; and in 1946, 19 per cent; a very definite downward trend in the school age group.

It is argued that this type of vaccination with certified vaccine from a central source, when inoculated intracutaneously, can be accomplished without causing severe local reactions. This method of prevention of tuberculosis in children in certain regional areas considered to be highly tuberculous, and from which there is no apparent escape (for instance Chinatown in San Francisco), has been advocated on a *volunteer* basis.

The really controversial issue in connection with the use of BCG is that of its ability to produce worth while and lasting immunity to clinical tuberculosis in the overwhelming majority of persons vaccinated and subsequently exposed to repeated or massive infection by virulent tubercle bacilli. The matter is still controversial. However, there has recently been added to the original "charter members" of an as yet unorganized club of enthusiastic believers in the vaccine, a large number of "associate members" who, previously skeptical, are now prepared to concede that the preponderance of evidence seems to indicate that the vaccine is "probably" of some value, and, being harmless, "probably" should therefore be offered to persons who are likely to be unavoidably and repeatedly or heavily exposed to tuberculous infection.

It is perhaps the public health worker's greatest mistake, in thinking of public health measures to control and prevent tuberculosis, to put a period instead of a comma after statistical studies, sanatorium facilities, tuberculin testing and X-ray confirmation. When this is done, and it is by no means an unusual circumstance, then the public health worker definitely establishes a mental terminus of the accumulated knowledge regarding tuberculosis. Perhaps in the past, false hopes have so misled the worker and the public that a defeatist attitude is ordinarily assumed.

The problem of control of tuberculosis in some areas of these United States, and certainly some other countries, may present such a dilemma, often financial, that between its horns the chasm is so wide that it is not a small wonder that the workers in the public health field fortify their hopes with the assurances that everything that can be useful is being done *correctly*. Every health official desires the reputation of broadmindedness, but quite often these officials are only passively curious.

Tuberculosis is likened to Emerson's *Life Is a String of Beads*, but this string runs out too fast before the entire knowledge is brought together for the common weal, and in order to fulfil our highest obligation to those unfortunately infected.

The use of BCG on the original principle, on nontuberculous children in a tuberculous environment from which there is no practical escape, as in Chinatown in San Francisco, comes the nearest to being a reasonable procedure. Therefore, the Department of Public Health of San Francisco and many San Francisco physicians concur accordingly.

For years, in international medical literature, the subject of BCG has been confused and controversial. It has attracted and held interest, but has yielded little usable substance.

Reports showed tremendous variation—variation in methods of application, groups served, in consistently controlled studies, and in the techniques of reporting results. With the exception of a few striking contributions, reports give only the number of vaccinations administered, and give general and not tuberculosis mortality and unfortunately do not employ life-table methods of analysis. In most cases, statistics have been incompletely collected and only partially analyzed. Though they often tell little, they tell it optimistically. Then there are the statistics based on studies too small to permit sound conclusions. Careful review of the total volume of literature published through the years following the initial work of Calmette and Guérin, in 1920, failed to reveal unquestionable proof of the effectiveness of BCG.

Observations in Canada, the United States, the Scandinavian countries and in South America suggest a relation between vaccination and decreased incidence of the disease in children over a short period of observation. Long-term protection has yet to be proved.

Studies by Ferguson in Saskatchewan, by Rosenthal in Chicago and by Aronson and Palmer among American Indians and Holm in Denmark have added greatly to our knowledge and to our hope that those unduly exposed to tuberculosis may have added protection.

Medical scientists in the United States have not been of one mind about the effectiveness of BCG as a protective agent. The advocates of BCG believe first that BCG can do no harm locally or generally to nonreactors to tuberculin. They believe, also, that vaccination with attenuated bovine tubercle bacilli induces the body to set up defenses in advance against a possible later virulent infection, severe enough to cause clinical tuberculosis. Opponents insist that only infected persons get clinical tuberculosis and disapprove, therefore, the deliberate imposition of even benign infection (although they fail to admit that many children inevitably get infected). Some of the tuberculosis clinicians in this country have strongly objected to infect any child who may have the chance of going through life without becoming infected.

The U. S. Public Health Service has been asked repeatedly to take a stand for or against BCG vaccination either for research purposes or for the protection of the community. We felt that we had insufficient factual data to state a definite policy at this time in regard to its use in this country. Meantime, tuberculosis was costing the Nation at least \$300,000,000 annually, and each year almost

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20,000 persons died outside hospitals and institutions—died without having hospital care during their terminal illness.

When one foreign country after another, and finally the World Health Organization group asked us to state our policy, the Tuberculosis Control Division knew that further deliberation would erroneously be interpreted as disapproval. It was plain that immediate action leading to a sound evaluation must be taken.

Following this decision, a conference on BCG was held in September, 1946 in the offices of the Tuberculosis Control Division of the U. S. Public Health Service. It was participated in by outstanding leaders in the field of tuberculosis in the United States, China and Denmark. The studies of Doctor Aronson and his coworkers were presented by Doctor Aronson and by Dr. Carroll E. Palmer who assisted in the analysis of these data. These were the American Indian studies, which, as you know, were carried on through the support of the Medical Research Committee of the National Tuberculosis Association. Dr. Johannes Holm presented his investigations and those of his coworkers in Denmark which have been carried on since 1930. After a detailed discussion of the material presented, there was a general discussion of the whole subject of BCG vaccination. Doctor Veldee, Chief of the Laboratory of Biologics Control in the National Institute of Health, presented the problems of virulence and stability of vaccine containing live organisms, and discussed the need for more research before commercial licensing of BCG could be considered. Further research was strongly recommended to determine the efficiency of the vaccination, and to attempt to develop a vaccine composed of dead bacilli. It was recommended that methods be developed to standardize techniques of preparation of a potent and stable vaccine for use throughout the world. Questions as yet unanswered satisfactorily are: How much immunity does BCG vaccination confer? How long does such immunity last? What are the long-time results?

Acceptable and usable answers to these questions will come only through co-operative research and frequent conferences by recognized research groups, and through the use of carefully controlled methods of study and of analysis. Any other plan will leave us just where we are for another twenty-five years.

As a result of deliberations by the conference, it was decided that the U. S. Public Health Service would conduct long-range studies to determine the effectiveness of BCG vaccination as an auxiliary method of tuberculosis control. It was decided that first consideration should be given to persons exposed so intensely that they are almost certain to become infected; and that we should particularly concern ourselves with special groups, such as the various tribes of American Indians, inmates and employees of mental institutions, employees of general hospitals and sanatoria (where danger of infection is excessive because control measures are lacking), medical students in schools where the services include exposure to tuberculosis patients, and persons economically and socially underprivileged, among whom tuberculosis mortality is high. It was planned that extensive studies in populous areas be initiated by the U. S. Public Health Service in co-operation with local groups. It was suggested that a country or

part of a State with a population of at least 100,000 people be studied over a period of several years.

One study was begun in April, 1947 in Muskogee County, Georgia, with headquarters in Columbus. When it was determined that a fair number of school children were negative to the tuberculin test and when approvals had been secured from their parents and physicians, BCG vaccine was given both white and Negro children. Splendid coöperation was received, not only from parents, but from the city and county school boards, the County Medical Society and the State Health Department.

The Columbus, Georgia study is the first in a series of long-range programs to be carried on coöperatively with recognized research groups throughout the country. The results should bring more than hope that BCG vaccination will supply the auxiliary methods of control so needed for the protection of young persons unduly exposed to tuberculosis.

## BCG VACCINATION

JOHANNES HOLM<sup>1</sup>

I shall try briefly to tell you about our views on BCG in the Scandinavian countries. As you know, we have been using BCG in the Scandinavian countries for more than fifteen years. In our countries BCG vaccination has passed the experimental stage and, as a matter of fact, it is not possible any longer to set up any controlled studies of BCG vaccination, because everybody who is a non-reactor to tuberculin wishes to be vaccinated. The vaccination is quite popular, not only among our specialists and general practitioners but also among the people.

As an illustration of the wide-spread use of the vaccination in Scandinavia, I can tell you that during the War the Swedish Army made BCG vaccination compulsory for all nonreactors. In Norway, at present a law is in process of enactment which will make BCG vaccination compulsory for nonreactors when they leave school and for other young adults. In all the Scandinavian countries, BCG vaccination is widely used. In 1946, more than one hundred thousand people were BCG vaccinated in Denmark.

I should like to say just a few words about our use of isolation before and after BCG vaccination, because I have a feeling that this has been misunderstood in this country. Real isolation of the vaccinated is used only when the mother of a new-born child has infectious tuberculosis. Here the child is taken away at once, sent to a children's hospital, vaccinated on the second day of his life, and kept in the hospital until the tuberculin reaction is positive—generally after six weeks. In other tuberculous families, we do not use any direct isolation of the vaccinated but try to obtain segregation. When a new case of infectious tuberculosis is discovered, the whole family is called in for an examination which always includes a tuberculin test. The infectious case is sent to a sanatorium for treatment and the nonreactors in the family are vaccinated before the infectious case returns to the home. The only reason for this isolation and segregation is to protect the reputation of the vaccine. We do not think it dangerous to vaccinate a person in the so-called preallergic stage of a virulent tuberculous infection; neither do we think it is more dangerous for a person to be infected just after he has had a BCG vaccination than if he had not been vaccinated at all.

In all the Scandinavian countries BCG vaccination is used primarily on young adults. Small children and even school children are generally not vaccinated unless they live in a tuberculous family or are otherwise especially exposed to tubercle bacilli. The number of cases of tuberculosis among children in Denmark is so small that it would be necessary to vaccinate several thousand just to avoid one case of tuberculosis, and the prognosis for cases in childhood is much better than for cases in adolescence. Among adults we do use BCG vaccination, even in areas where the tuberculosis infection rate is very low, just as low or even lower than in Minnesota.

The general opinion in the Scandinavian countries is that BCG vaccine is an excellent weapon in the fight against tuberculosis. But, this weapon must be used together with all the other measures for controlling tuberculosis.

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## BCG VACCINATION

J. ARTHUR MYERS<sup>1</sup>

At present BCG is such a highly controversial subject that it would seem unwise for anyone to tell another why he should or should not use this organism in an attempt to protect humans against tuberculosis. Therefore, in this presentation I am offering no advice whatsoever to others. Personally, I am enthusiastic about the use of BCG under only one condition, namely, the studies now in progress by the Tuberculosis Control Division of the United States Public Health Service. I have every confidence that those in charge of this work will conduct a highly scientific and thoroughly controlled study on a limited number of people over a sufficiently long period of time to establish facts. If these studies prove beyond all doubt that BCG is thoroughly efficacious as is smallpox vaccine, I would be among the first to recommend its universal use and even to seek methods for making its administration compulsory. Until that time arrives, however, I shall not employ or recommend BCG for the following reasons:

(1) Our knowledge of immunity in tuberculosis is woefully inadequate. We do not know how much or how little develops from an actual attack of the disease. We do know, however, that whatever immunity develops is not dependable. It is only the persons who have had primary tuberculosis, demonstrated by the tuberculin reaction or at the postmortem table, who develop clinical destructive forms of the disease. With these facts in mind, I do not find a premise from which to start artificial immunization with living organisms of reduced virulence, whether they be BCG, vole bacillus or any other.

(2) BCG has failed to adequately immunize animals against tuberculosis. The most that has been found is that it slows the early progress of the disease. In the majority of the experiments reported, the inoculated and the control animals were killed too soon. While it is true that more tuberculosis was present in the controls, there was always disease in the inoculated animals. If all animals were allowed to live, the controls would die first, but the inoculated animals would later die just as surely from tuberculosis. The veterinarians of this country, after adequate trial, found BCG inefficacious in controlling tuberculosis in cattle. They then proceeded with proved, fundamental methods and have almost eradicated the disease from the 68 million cattle of this country.

(3) If BCG were highly efficacious, an abundance of convincing proof should be available after more than a quarter of a century of use and having been administered to approximately seven million people. It should not now be controversial. In the nations where it has been most extensively used I have found no evidence of its effectiveness on tuberculosis morbidity and mortality. Far greater reductions in these rates have occurred in parts of the world where BCG has not been introduced.

(4) To this moment BCG administration must be regarded as wholly experi-

<sup>1</sup> University of Minnesota Medical School, Minneapolis, Minnesota.

mental. To me the health and lives of people are too precious with regard to tuberculosis to justify experimental procedures. The only exception is a highly scientific, thoroughly controlled experiment on a very limited number of people, such as that now in progress by the United States Public Health Service. Here, there is no danger of the development of a false sense of security among the public or neglect and abandonment of fundamental procedures. The inoculated will be watched as carefully as the controls.

(5) It has not been proved to my satisfaction that BCG is harmless. While there is apparently no immediate danger from the inoculation, no one has yet proved that the organisms may not survive in the bodies of some persons for many years or decades and gradually regain their virulence. The ancestors of these organisms were virulent, and there is no proof that, given time in human tissues, the descendants of the present avirulent organisms cannot regain that virulence. Opinions have been expressed to the contrary, but they are *only* opinions.

(6) The favorable reports that have appeared in the literature have, with rare exceptions, been from inadequately controlled studies. Moreover, there is no study reported that has been in progress sufficiently long to determine how BCG affects tuberculosis in a sizable group of persons observed from infancy throughout the span of life.

(7) Wherever favorable reports have been made the diagnostic criteria employed can be questioned. For example, erythema nodosum has been regarded as clinical tuberculosis. Most diagnoses of pulmonary lesions have been made from X-ray shadows alone, and in many cases on such flimsy evidence as apparent enlargement of hilar shadows. In several instances there has been no attempt whatever to differentiate between the primary and the reinfection type of disease. Among the controls, those with primary lesions are grouped with those with the reinfection type and compared with lesions found in the inoculated, which must be only of the reinfection type. Therefore, deductions have been drawn from the comparison of unlike conditions. All too often postmortem examinations have not been made of the controls or vaccinated who were thought to have died from tuberculosis.

(8) Since Falk inoculated animals with tuberculous tissue to weaken bacilli by putrefaction in 1883, the tuberculosis world has been thrown into a state of ecstasy on several occasions, only to be disappointed in a few years. There are a few persons in the world who are wildly enthusiastic about BCG. However, their judgment, training, scientific experience and accomplishments probably are not superior to those of other great men in the field of tuberculosis, such as Koch and von Behring, who were just as enthusiastic and as absolutely certain that they had discovered efficacious immunizing agents against tuberculosis. There have been large numbers of these workers in each decade since 1883, but not one of the agents produced has stood the test of time, and some of them were not so different from Calmette's method. Each one has started on the same shaky premise, namely, that an actual attack of tuberculosis does not produce dependable immunity.

(9) By using fundamental, well established and dependable methods we have brought tuberculosis under control among our students of nursing and medicine, and in the public at large far more satisfactorily than anyone has ever done through the use of BCG. Until someone can show that BCG is superior or even equal to our methods, I can see no advantage in using it. In one of our schools of nursing, where from 10 to 19 per cent of the students developed demonstrable lesions in the 1920's and early 1930's, there has been only one student in the past four years who presented such a lesion. In our school of medicine only one has developed a lesion that could be detected by X-ray inspection in four years. Both the student of nursing and the student of medicine reacted to tuberculin on entrance to their respective schools.

(10) The tuberculin test is my most potent weapon against tuberculosis. It is not only absolutely essential to me in the diagnosis of cases of tuberculosis, but it is the procedure that leads me most often to the unsuspected, contagious case of tuberculosis. Moreover, it is the only procedure by which I can actually determine with accuracy the effectiveness of a tuberculosis control program from time to time. If BCG were to be administered to a considerable number of our children and young adults, thus sensitizing their tissues, the tuberculin test as we now use it would be nullified, and our present effective program would have to be abandoned.

There are two physicians in this audience (Slater and Jordan) in whose sanatorium districts there are now large areas in which they have completely eradicated tuberculosis at the grade school age level. No BCG has ever entered either district. This accomplishment, which should be the ultimate goal of every tuberculosis worker, was made by standard, thoroughly tried and unfailing methods.

(11) I am unwilling to make a truce with the tubercle bacillus. As far as is now known, BCG does not prevent virulent tubercle bacilli from entering the human or animal body nor does it destroy them after they enter. Indeed, in most of the larger series of cases reported, clinical lesions have developed and deaths have occurred among the vaccinated.

(12) Reactions to statements recently made in the lay press indicate that a sense of security is already developing in the public mind which, if allowed to continue, could bring about almost if not complete cessation of interest in the fundamental procedures by which so much has been accomplished in this country. The fine coöperation now being manifested by the public could quickly be lost and, thus, the clock of tuberculosis control could be set back by half a century. When the physician uses the words vaccination and immunity, the public thinks of total protection as in smallpox. To date I find no reason for even intimating such security from the use of BCG.



## BCG VACCINATION

### SOL ROY ROSENTHAL<sup>1</sup>

The Tice Laboratories of the Chicago Municipal Tuberculosis Sanitarium, in coöperation with the University of Illinois College of Medicine, have been in continuous operation for the production of BCG vaccine in Chicago for the past thirteen years. Vaccination of humans began ten years ago and has continued uninterruptedly. This constitutes the longest continuous experiment in the United States. The culture which has been used during all this period is the one that I brought from the Institute Pasteur in Paris. In following the meticulous method prescribed by the Institute Pasteur, I found no variation in the growth of the organisms, in the type and extent of lesions produced by them and in the tuberculinization of animals and humans.

The clinical application of the vaccine was begun on the major premise that BCG is to be used as a supplement to the already existing methods of control so well formulated by this Society. BCG was not to be considered as a panacea for tuberculosis prevention.

In order to establish whether or not the various age groups would benefit by this form of vaccination, the following carefully controlled studies were undertaken:

- 1: New-borns originating from a highly infected environment but where no tuberculosis was present in the immediate household as determined by X-ray examination of the chest of each member.
- 2: New-borns originating in households where tuberculosis was present.
- 3: Nursing students.
- 4: Medical students.
- 5: Children of all ages in Government housing projects.
- 6: Inmates of insane asylums including the aged.

The results for the first two groups only will be given in detail. It is of interest to know, however, that, from the available evidence to this date, there has not been a case of pulmonary tuberculosis in any of the vaccinated of all the groups studied. During a ten-year period there were approximately 1,400 vaccinated and 1,400 controls in group 1. Each group was followed for, approximately, 6,000 person years. In the vaccinated group there were 11 cases in which the X-ray film of the chest revealed lesions which were considered to be tuberculous. Only one case needed hospitalization and this child died. The remainder recovered spontaneously. The case that died failed to react to the Vollmer patch test six months after vaccination, an exceedingly rare occurrence. On repeating the patch test, however, a positive result was obtained. At fifteen months the reaction was again negative and again at eighteen months it was weakly positive.

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In a reconstruction of this case, it can be considered as one which did not "take" or, at best, was a poor "take." The child died of a tuberculous meningitis following a typical primary complex of the lung. There were no lesions at the site of inoculation or of the draining lymph nodes.

Among the controls, there were 39 cases of tuberculosis of which 15 were hospitalized and 7 died. The death rate from tuberculosis, per 1,000 person years observation, was for the vaccinated 0.17 and for the controls 1.16.

In the group of children where there was tuberculosis in the family, both the vaccinated and the controls were isolated in foster homes until the tuberculin test was positive. Of the 151 vaccinated, there were 2 cases of tuberculosis and no deaths. Of the 105 controls, there were 5 cases of tuberculosis with 4 deaths.

Considering both groups as one, there was one death in the vaccinated group against 11 in the controls.

The method of vaccination used was one which was developed by this laboratory and is called the multiple-puncture method. It consists of placing a drop of vaccine on the outer aspect of the alcohol-cleansed arm through which 30 punctures are executed over an area of 2 x 2.5 cm. A sewing type needle similar to the one used for vaccinia is held tangentially to the skin and enough pressure is exerted so that the point of the needle engages the skin. The punctures are placed approximately 2 to 4 mm. apart in three rows of ten punctures each. Following this method, the local reactions are practically insignificant and the complications are nil. Tuberculinization occurs for practical purposes in all cases (99.4 per cent) within a period of a month. After six and a half years 80 per cent still react to the Vollmer patch test and 1 mg. of OT following a single vaccination. This method or its modification has been used extensively in France, Norway, South America and Asia. It is preferable to the intracutaneous method because the latter produces a local ulcer which drains for weeks to months.

The Tice Laboratory has been selected as the central one for BCG production for the United States Public Health Service. In this capacity it has supplied vaccine for the Government BCG vaccination programs in the states of Georgia and Michigan.

In summary, BCG vaccination is of decided value in protection against tuberculosis. The vaccine should be considered as a supplement to the already existing control measures for the prevention of tuberculosis. The multiple-puncture method is recommended because it produces rapid and uniform tuberculinization and is devoid of complications.

## DISCUSSIONS<sup>1</sup>

### BCG

HECTOR ORREGO PUELMA<sup>2</sup>

Our experience with BCG in South America is extensive as regards the number vaccinated but rather limited as regards the follow-up observation of the cases.

However, we are in a position to state that BCG has proved completely innocuous in all cases that have been followed up, and that it has a very definite value in increasing resistance. This is demonstrated particularly clearly in the milder clinical course of primary infections in vaccinated children, who are exposed to open tuberculosis.

As regards the various techniques suggested for the vaccination, we have the impression that Rosenthal's multiple-puncture method is more effective in that its results are more certain and more lasting.

In summary, we feel obliged to state that, although BCG is of real value in tuberculosis prophylaxis, it cannot replace the usual method of isolation and early diagnosis and treatment, and that its immunizing action is not able to combat massive doses of the tubercle bacillus.

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### BCG

S. A. SLATER<sup>3</sup>

The old saying that everything that glitters is not gold is quite true. After many years' experience in tuberculosis work I have seen things that have come upon the horizon heralded as a preventive or cure which sparkled for a while and then faded out. This may be true of BCG. Time and much work are yet necessary before its value is proved.

All admit, I am sure, that infection with tubercle bacilli is necessary before clinical tuberculosis can be produced. We also know that all who become infected do not break down. The reason some do and some do not is still unknown. It would, therefore, seem much more sensible to prevent any infection, regardless of its strength, entering one's body.

The use of BCG would destroy the value of a most potent weapon in finding those who are infected with tuberculosis—the tuberculin test. The method we have used is to find those who are infected and, if possible, the infecting source and properly take care of both. This method has brought the death rate down to one-seventh of what it was in 1920 and the frequency of a positive tuberculin test to less than 10 per cent among high-school students. I realize that all parts of the country are not so fortunate that this method can be used effectively, but they should work to get themselves in a position where it would be practical rather than using a method rendering everyone tuberculin-positive, thus destroying one of the most potent weapons against tuberculosis. I am not absolutely against the use of BCG under all conditions but feel we are in need of better proof of its value and that its use should be limited to well controlled groups. Infection carries the thought in

<sup>1</sup> Presented before the Medical Section, as part of the *Seminar on BCG*, at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 19, 1947.

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<sup>3</sup> Worthington, Minnesota.

the public mind of disease, vaccination carries the thought of prevention. Until we have better proof that BCG is of real value we should use the term infection with BCG rather than vaccination.

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### Closing Remarks by the Moderator

From the various discussions given this morning, as well as opinions gained from other data, it seems clear that, if rigidly supervised, BCG has a place in antituberculosis work. There can be little doubt that it raises the threshold of infectability in the vaccinated so that nurses, attendants, internes and others exposed to tuberculous infection are better protected than the unvaccinated. There may be a limited and temporary use, or both, in badly contaminated regions, especially in war-torn countries, to protect infants and young adults against infection where the public health facilities have completely collapsed. In such circumstances, however, it should be used only as an emergency measure and supervised competently.

There appears to be little gained in indiscriminate use of the vaccine and much may be lost. It may develop a false sense of security so that lay people and physicians may rely too much on it and not enough on tried and proved public health methods. Because it is cheaper, it will have an appeal to public officials who are generally attracted to the less expensive methods irrespective of efficiency. It is also unnecessary in most progressive countries because the death rates are falling fast, and the control of the disease seems assured by the regular public health methods.

Finally, in some localities where the incidence of tuberculin reactors is low, there is a distinct advantage in leaving the noninfected cases anergic, not only for the diagnosis of tuberculous infection, but also for diagnosis of nontuberculous diseases. Since a negative tuberculin reaction is one of the most valuable aids available in the diagnosis of nontuberculous diseases, it would seem advisable not to create artificially positive reactions where it is not absolutely necessary.



# THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

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**Treatment of Emphysema.**—Experience shows that medication in pulmonary emphysema is purely sedative and transitory. Surgical measures, as suggested from time to time, have not fulfilled the hopes of their advocates. Recent physiopathological studies permit facing the problem from a different angle. The use of special belts increases intraabdominal pressure and tends to replace the diaphragm in its normal position and further its motility. Pneumoperitoneum has been tried with apparent success in a limited number of cases. In 2 cases reported here this method brought about a marked increase in vital capacity and an elevation of the diaphragm. Pneumoperitoneum has its uses and may solve the palliative problem when applied in proper cases. In advanced obstructive cases little can be done.—*Cómo encarar el tratamiento del enfisematoso pulmonar*, J. Armando Sciuto, *Rev. de tuberc. d. Uruguay*, December, 1946, 14: 237.—(A. A. Moll)

**Broncho-monilliasis.**—The chest roentgenogram of a 36-year-old farm laborer with febrile erythema nodosum showed bilateral, spotty shadows and large lymphomata in the right hilum. The Mantoux test was negative. Four months later a pleurisy developed, and, again, a Mantoux test was negative. Histological changes found in the tonsils were considered characteristic for sarcoidosis. Serum albumin was 8.4 per cent with 4.37 per cent albumin and 4.03 per cent globulin. Guinea pig inoculation with sputum and gastric lavage fluid showed no tubercle bacilli. A profuse growth of *Monilia*, type *mortifera*, developed in Löwenstein's medium, and after two

months' culture on Sabourraud agar there appeared numerous acid-fast elements. Guinea pig tests with the fungus and its acid-fast component were negative. In the tonsils from this patient both single fungus cells and small colonies of acid-fast rods were found, as well as some cones of the type described by Hallberg and thought by this author to be derived from fungus cells. In addition, two free lying formations were found in the tonsillar crypt, consisting of a vegetable stroma in which numerous acid-fast rods were lying. Intracutaneous injections of a solution prepared from a heat-killed Sabourraud agar culture produced only nonspecific changes in the patient. "It has not been possible to obtain any support for the theory of Törnell that the very common monilia saprophytes or their acid-fast transient forms should have any etiological significance" in sarcoidosis.—*Moniliasis in Lymphogranulomatosis benigna*, L. E. Warfvinge, *Acta med. Scandinav.*, 1947, 127: 286.—(O. Pinner)

**Intratracheal Penicillin in Bronchiectasis.**—Thirteen adults with chronic suppurative bronchiectasis and one child with suppurative pneumonia and early bronchiectasis were treated with intratracheal instillations of penicillin. Seven to 15 instillations of 100,000 units of penicillin in 20 cc. saline solution were given over a period of eleven to eighteen days. Ten of the thirteen patients with chronic bronchiectasis had a drop of 50 per cent or more in the volume of sputum in twenty-four hours following the instillations. The reduction of sputum was beyond that obtained previously by injections of penicillin, nebulized penicillin or sulfonamides. Recurrence of

symptoms within two months was seen in 4 patients. Intratracheal penicillin therapy is advised for the preparation of patients for lobectomy. One child with suppurative pneumonia and atelectasis of more than three months' duration experienced immediate and lasting clearing and reexpansion of two lobes after intratracheal instillation.—*Intratracheal Penicillin Therapy in Suppurative Bronchiectasis*, L. E. Siltzbach, *Arch. Int. Med.*, May, 1947, 79: 570.—(G. C. Leiner)

**Surgery for Bronchiectasis.**—Fifty patients with bronchiectasis were treated by pulmonary resection. There was no postoperative death. Five patients developed empyema, 2 a bronchopulmonary fistula and one thrombophlebitis. Forty-two patients were able to resume normal activity.—*Appraisal of Surgery in the Treatment of Bronchiectasis*, R. Adams & B. J. Ficarra, *J. A. M. A.*, May 17, 1947, 134: 240.—(H. Abeles)

**Intrabronchial Penicillin and Sulfonamides.**—Twenty patients with suppurative pneumonia and lung abscess, 16 with bronchiectasis and 2 with infected cystic disease, were treated with intrabronchial administration of penicillin and sulfanilamide. Each of these drugs was suspended in 40 per cent iodized oil and these suspensions were mixed to make a concentration of 3,000 units of penicillin and 0.1 g. of sulfanilamide per cc. In 14 cases of lung abscess with pneumonia the suspension was administered to enter the diseased area; 10 were cured, 3 improved and one died. In this group there were 7 cases with a single lung abscess and 7 had extensive pneumonia with several cavities. In cases of the latter type simple surgical drainage is not practicable, while the only alternative, lobectomy or pneumonectomy, may have a high mortality in toxemic and debilitated patients, so that successful medical treatment is of utmost importance. From 2 to 10 instillations, with an average of 4.4, were given in this group, and in several cases a dramatic result was noted after a few applications or the patients soon felt so well that they refused further treatment. In those

cases where it was possible to do a follow-up bronchogram, residual minor bronchiectasis without symptoms except for an occasional cough was always found. In the remaining 6 cases of lung abscess and pneumonia, the suspension failed to enter the diseased area; of these patients one was cured, one improved but subsequently died from unknown cause and 4 died. Some therapeutic effect of the penicillin absorbed from the bronchi near the affected area is possible but if adequate filling is not obtained after 2 or 3 instillations it is wiser to abandon the attempt and adopt other measures. In one of these cases penicillin was twice injected into a giant abscess through the chest wall, and when this proved to be ineffective, rib resection was performed; this patient died three days after operation. It is unlikely that so large an abscess can be cured by penicillin whatever the method of administration; it should be drained surgically without delay. Sixteen cases of bronchiectasis and 2 of infected cystic disease were treated with the same intrabronchial method using 3 instillations at intervals of from six to twelve weeks. This course was repeated when symptoms recurred. Fourteen patients had considerable relief, in 4 cases the benefit was slight to moderate. Some cases had as many as 25 instillations during eighteen months. In another group of 15 cases with bronchiectasis previously treated with sulfanilamide in lipidol, 3 patients subsequently had to have a lobectomy, and 8 others were later on treated with the sulfanilamide-penicillin suspension; in these the combined treatment was symptomatically superior to the sulfanilamide alone. This treatment of bronchiectasis is indicated (1) in cases with minor degree of bronchial dilatation, not severe enough to warrant lobectomy, (2) where the extent of the disease or the general condition counterindicates lobectomy, or when the patient refuses operation, (3) to sterilize the bronchi and improve general health in preparation for lobectomy. As yet no signs have been observed that the infecting organisms have become penicillin-fast by repeated application.—*Intrabronchial Administration of Penicillin and Sulfonamide*, B. A.

Dormer & F. J. Wiles, *Clin. Proc., J. Cape Town Post-Grad. M. A.*, March, 1947, 6: 10.—(O. Pinner)

**Mediastinal Emphysema.**—A 16-year-old Negro boy with spontaneous mediastinal emphysema was seen. Hamman's sign, fever and leucocytosis were present. The roentgenogram revealed air in the anterior and posterior mediastinum. The electrocardiogram showed signs of right axis deviation and of acute right ventricular strain. Ten days later the electrocardiogram had become normal.—*Spontaneous Mediastinal Emphysema with Acute Right Ventricular Strain*, A. Klein, *Am. Heart J.*, June, 1947, 33: 367.—(G. C. Leiner)

**Spontaneous Pneumothorax.**—Retained gas in various portions of the body, such as intestinal gas or subcutaneous emphysema, is composed chiefly of nitrogen. In these conditions, when the patient inhales 100 per cent oxygen, blood coming into contact with this oxygen in the lungs gives off most of its nitrogen. In a short time, the retained nitrogen is all dissolved in the blood and then given off in the alveolar air which is almost entirely oxygen. The author reasoned that this principle might be used in the treatment of spontaneous pneumothorax. In one patient, the inhalation of 100 per cent oxygen for two or three hours several times daily over a period of twelve days apparently resulted in a more rapid reexpansion of the lung. The inhalational therapy also produced immediate relief of chest pain. Further controlled use of this treatment is suggested.—*Oxygen Inhalation in the Treatment of Spontaneous Pneumothorax*, E. Press, *Ann. Int. Med.*, July, 1947, 27: 135.—(H. R. Nayer)

**Treatment of Empyema.**—Gramicidin is a biological antiseptic. It was found to have a stronger effect upon staphylococci than tyrothrycin. Alcoholic solutions remain stable for many years. Thirteen cases of empyema were treated by instillation of a gramicidin solution after aspiration of pus. In the cases caused by gram-positive organisms, there was obvious improvement after two to three treatments.

By the eighteenth day, no pus was evident. The treatment was ineffective in cases of tuberculous or putrid empyema.—*Treatment of Purulent Pleurisy with Gramicidin*, M. I. Lavrentyeva, *Am. Rev. Soviet Med.*, June, 1947, 4: 397.—(A. G. Cohen)

**Hydrothorax in Liver Cirrhosis.**—Massive hydrothorax with no recognized etiological basis other than cirrhosis of the liver is rare. Six cases were found on autopsy among 600 cases of cirrhosis of the liver. Two cases are described in detail. The fluid was present in one case in the right pleural cavity only, in 2 cases in the left pleural cavity only and in 3 cases in both pleural cavities. The fluid had the characteristics of a transudate. The mechanism of the development of pleural fluid in these cases remains unexplained.—*Cirrhosis of the Liver with Massive Hydrothorax*, D. G. McKay, H. J. Sparling & S. L. Robbins, *Arch. Int. Med.*, May, 1947, 79: 501.—(G. C. Leiner)

**Collapse of Cava Superior.**—X-ray studies with 40 per cent sodium iodide solution in dogs showed that the distension or collapse of the upper vena cava does not depend on a lowered pressure in the thorax. It is actually related to the position of the animal at the time. The vein collapses when the head is up, and distends in the vertical position when the head is down. During two pleuroscopies in man confirmation of these experiences was found, the vein collapsing or distending as the position of the head changed.—*Sobre el estado de distensión o colapso de la vena cava superior*, J. Duomarco, R. Rimini & F. N. Fredari, *Rev. de tuberc. d. Uruguay*, September, 1946, 14: 151.—(A. A. Moll)

**Diagnosis of Amyloidosis.**—The problem of diagnosis of amyloidosis has always been important in the management of certain chronic diseases, especially tuberculosis. In the latter, it is probably more common than is supposed as recent reports are similar to that from Sea View Hospital, in which amyloidosis was found in 22 per cent of 2,000 consecutive autopsies. Until Bennhold introduced the Congo red test



in 1923, the diagnosis was difficult and uncertain. However, difficulties have been apparent from the first, especially because of false positive tests. It is believed that the trouble lies in interpretation of the test, that is, that 90 to 99 per cent adsorption of the Congo red is only suggestive of amyloidosis, but that 100 per cent is very suggestive of amyloidosis. Also one test only cannot be relied upon. Therefore it is essential that the test be repeated at least once. The author has found that, when there is complete or nearly complete absorption of the dye on repeated tests, amyloidosis has always been found at autopsy. False negative tests will occur when there is only a small amount of amyloidosis present.—*The Diagnosis of Generalized Amyloidosis by the Congo Red Test: Definite Diagnostic Criteria*, I. J. Selikoff, *Am. J. M. Sc.*, June, 1947, 213: 719.—(G. F. Mitchell)

**Histoplasmin Sensitivity.**—The conditions which produce histoplasmin sensitivity are still unknown although it seems reasonable to assume that the reactions and associated pulmonary lesions are specific evidence of some kind of infection. If the several members of a family were to show similarity in their skin reactions the implication would be that the agent producing sensitivity is present (or absent) among conditions affecting members of a family group. This condition could be genetic, broadly environmental, or specific environmental factors localized in the home. From a material of about 16,000 school children skin-tested with tuberculin and histoplasmin, 1,744 cases were analyzed, comprising 766 children who had older siblings who reacted to histoplasmin, and 978 with an older sibling who did not react; only white, life-time residents of the metropolitan area of Kansas City, Missouri, were considered in this study. A detailed, mainly statistical evaluation of all data involved shows: The percentage of reactors is higher among children whose older sibling is a reactor than in the group without reacting siblings, that is, there is a similarity in the histoplasmin reaction between children of the same family. This difference in the percentage of

reactors between the two groups decreases with increasing age of the older child, and the degree of similarity is further influenced by the closeness in age of the siblings. When there is no more than two years' difference in age, the differences in reactors among siblings of a reactor and a nonreactor are greater. After elimination of those factors (geography, age, sex, race) known to affect the frequency of histoplasmin reactors, there remains some factor which makes siblings of a reactor more likely to react than siblings of a nonreactor. Other factors causing variations in histoplasmin sensitivity may well be disclosed by further detailed study. The fact that in Kansas City there was not a high concentration of reactors in some families and of nonreactors in other families suggests that there is implied a factor broader, and less localized, than one limited by familial environment.—*Histoplasmin Sensitivity among Siblings*, Shirley H. Ferebee & M. L. Furcolow, *Pub. Health Rep.*, June 6, 1947, 62: 834.—(O. Pinner)

**Epidemiology of Tuberculosis.**—The contagious nature of tuberculosis was known many centuries B.C., as recorded in writings from India and Greece. In later centuries these early ideas were forgotten, and not until toward the end of the 17th century did the scientists of the Latin countries again recognize the contagious nature of the disease. Edward Mainwaring wrote in 1667: "You must not frequently converse with a phthisical person whose unwholesome breath may infect the sound by drawing in putrid vapours which the other breathes forth, but above all a phthisical bedfellow is most dangerous to affect a sound person and chiefly to be avoided." However, men such as Bright, Addison and Graves disregarded the contagious nature of tuberculosis and attached great importance to diathesis. Even Laennec did not believe that tuberculosis was contagious. In later years, in spite of the acceptance of the idea that the human tubercle bacillus was the infecting agent, it was difficult to prove and have accepted the idea of the contagious nature of the bovine bacillus for

man. It is now generally agreed that only two types, the human and the bovine, are causative agents of human infection, although the avian type may rarely be the cause. It has been shown that man can contract the disease from cattle and likewise can infect cattle. The infection of cattle may be by either the human or bovine bacillus. The chief pathway of infection for tuberculosis in man is the respiratory system. Other pathways may be through the gastrointestinal tract. Droplet infection is usually the source of the human tubercle bacillus. Tubercle bacilli may be inhaled without producing any recognizable lesion, and it must be assumed that in these cases the tubercle bacilli are destroyed. Both native and acquired resistance are the factors which prevent the disease from assuming epidemic proportions. From Lurie's work, it would appear that cellular resistance is more important than humoral. The source of human infection in childhood is usually a near relative. Repeated exposure and quantity of bacilli are the important factors in producing an infection, either one of which factors may overcome resistance. The primary infection may result either in a child or in an adult. It was observed that during the war more primaries appeared in adults, probably because of the migration of rural dwellers to industrial urban areas. In the child the lymph nodes usually show greater involvement than the lungs, and it is thought that this depends on the degree of hypersensitivity which the child has developed in the interval occurring between the lapsing of the lesion in the lungs and that in the nodes. In the older child, the tracheobronchial nodes contain less tuberculosis, and this is also true in the adult. This absence of secondary lesions in the nodes of older children and adults may partly be accounted for by the more frequent evidence of healing, as judged by the growth of fibrous tissue around the primary lesion. Age is undoubtedly an important factor in determining healing; the longer the primary infection in the child is delayed, the greater the chance of resolution. If the disease is not localized at or near the sight of

infection, then in the child generalization occurs, resulting in acute generalized miliary tuberculosis, with or without tuberculous meningitis. The first infection in the lungs is on virgin soil. In most cases localization takes place. The patient has now developed hypersensitivity, which tends to lessen as age advances. The tissue reaction to reinfection tuberculosis depends on the degree of hypersensitivity, the immunity, dose and virulence of the infecting bacilli. In general, infected animals in which hypersensitivity has waned have acquired a high degree of resistance to any subsequent infection. The resistance is by no means absolute, and it may be broken down by acute or chronic disease, overwork and malnutrition. A high degree of hypersensitivity is an unfavorable factor, as demonstrated in animals. Alimentary infections occur by swallowing contaminated food, and in children by contaminated fingers from the floors on which droplets of sputum have been present. Imperfect cleansing of eating utensils may be the source, also. Tuberculosis of the cervical nodes is caused in the greater proportion of cases by the bovine type in countries in which tuberculosis in cattle is frequent. This holds also for primary intestinal infection. The more frequent occurrence of catarrhal conditions in the nasopharynx in childhood may act as a *locus minoris resistentiae*. The possibility of acquired resistance due to an arrested infection in the lungs may also determine the relative infrequency of alimentary tuberculosis in the adult. The rural inhabitant is more liable to bovine infection than the urban. In tuberculous meningitis, 8 per cent were infected with bovine strains in large burghs and cities of Scotland, as against 15.9 per cent in the rural areas of the counties. In those areas in which there are attested herds, the incidence of bovine tuberculosis is definitely less. It is also shown that in the cities where heat treatment of milk is used the incidence of bovine tuberculosis is less. It is felt that because of the large percentage of human infection in the urban areas, the acquired immunity thus reduces the chance of bovine

infection. Respiratory infection of bovine origin is rare but has occurred. The ideal, of course, is that all milk for human consumption should come from attested herds, but in Britain this is a long-term policy. In the meantime, heat treatment should be used. It is felt that BCG vaccination is still a controversial question.—*The Epidemiology of Tuberculosis*, J. W. S. Blacklock, *Brit. M. J.*, May 24, 1947, 4507: 707.—(R. W. Clarke)

#### Tuberculosis and General Practitioner.—

The private physician is the principal force in the control of tuberculosis and case-finding. Mass radiography is far superior to other approaches to tuberculosis control, such as examination of contacts of known cases which discovers as little as 25 per cent of new cases reported each year, or annual tuberculin-testing of the whole population which has been shown to be impracticable. By mass radiography teams the communities of the United States could be covered in less than five years, a short enough span of time to prevent the disease from spreading to a new generation. With this new method 65 to 70 per cent of all cases found have minimal lesions, while in recent years only 10 per cent of hospital admissions had minimal disease. Newly discovered cases and their families go to their family physicians for supervision, care and the necessary long-term follow-up. Intracutaneous tuberculin testing and X-ray examination on every not recently examined patient should be fundamental routine for the physician; the films should be interpreted in conferences with experts. Sputum examination of all patients with cough or expectoration will reveal 3 or 4 per cent positive specimens. In less populous areas the physician has to carry on case-finding and follow-up almost single-handed, and knowing his patient's personality he will know how to encourage him in the crisis often occurring upon the announcement of tuberculosis. His interest and his effectiveness as a worker in the community-wide program of tuberculosis control will grow as he learns of the latest advances in this field. Some of these de-

velopments are enumerated in detail in this paper: the great variation in tuberculin sensitivity depending on the dosage used and the characteristics of the population group tested; the frequency, in certain parts of the country, of pulmonary calcifications among nonreactors to tuberculin who react to histoplasmin; the use of the photofluorograph and the attempts to determine, by group work, the human error in the interpretation of chest films; BCG vaccination; the dangers for tuberculosis control arising from streptomycin treatment and the necessity in spite of the use of chemotherapeutic agents to provide more beds for isolation and treatment; the importance of laboratory examinations for tubercle bacilli; pneumothorax and surgical therapy; epidemiology; the unsolved problem of the hospitalization of the tuberculous, due to the insufficient number of beds available especially for minimal cases. In this latter respect it is suggested that the clinically not active cases should be supervised and minimal cases of uncertain or active status and the more advanced cases should be hospitalized; the remediable positive-sputum cases should be hospitalized first, the irremediable positive-sputum cases should be isolated in a single room in a general hospital during the terminal episode, or, if this is impracticable, the hopeless case must be cared for in the home under the best possible isolation technique. We must think of the community first and of the individual next when hospital beds are restricted. The private physician has a certain public as well as private responsibility, and, in this connection, his importance as a factor in promotion of public health and his duty of reporting to the health department all his tuberculous cases and his delinquent patients are stressed. His participation in the official field studies, the routine use of the tuberculin tests on every patient in rural districts, the examination of family contacts and the search for the original spreaders would assist in epidemiological investigation. The cost of such a rapidly expanded program will be high as a short-time expenditure but low when compared with the cost of control over a

period of several decades and with the savings in sickness and death to be accomplished by such a plan. In order to conquer the disease, the standard of living must be greatly improved, especially among many of the non-white groups of the population.—*Community-wide Chest X-ray Surveys and the General Practitioner*; H. E. Hilleboe, *Journal-Lancet*, June, 1947, 27: 225.—(O. Pinner)

**Tuberculosis Control.**—Among the diseases now epidemic in war stricken areas, tuberculosis has again become a fearful problem. Disease is not hampered by barriers, thus it is in the self-interest of relatively healthy and well-fed nations to prevent the spread of tuberculosis in any area. The United States has not been directly touched by the war; indeed, through the war years tuberculosis has continued to decline. But this happy circumstance is not wholly the consequence of our fortunate situation. A historical survey, given briefly in this paper, shows the continuous efforts of private and public agencies to control and finally eradicate tuberculosis in this country. Since its establishment on July 1, 1944, the Tuberculosis Control Division of the United States Public Health Service has been guided in this fight by four major principles: (1) case-finding; (2) medical care and isolation; (3) after-care and rehabilitation; (4) protection of the tuberculous patient and his family against economic distress. Case-finding, recently using the miniature X-ray film, reaches large groups of the population—more than 25 million persons by the end of 1946—and thereby discovers minimal lesions; while in former years only 10 per cent of admissions to tuberculosis hospitals were minimal cases, now 70 per cent of all new cases found are minimal. Industrial workers as a group have been one of the chief interests of the Tuberculosis Control Division; a program is under way to provide for routine X-ray examination of a second large group, namely, all patients, out-patients and employees coming into general hospitals. Medical care and isolation of infectious cases must not be delayed by inadequate sanatorium

care. However, in America we are faced with the problem of providing at least 50,000 additional sanatorium beds. As mass radiography detects larger numbers of patients with early disease, shorter periods of hospitalization than necessary under the present circumstances will frequently be the rule. Such persons need only enter convalescent homes for the transition period or may be regularly transferred to the chest clinic. After-care and rehabilitation, medical, social and financial guidance are often necessary for several years after discharge from the hospital. Sooner or later, it will be necessary to provide invalidism insurance for these people. Economic protection of the patient's family almost invariably resorts to public resources. Generous assistance has to be given needy families in order fully to utilize the benefits of other control activities; tuberculosis and poverty are often associated. "A national plan to provide adequate insurance for the family against loss of wages during the period of prolonged sickness is the only realistic answer to the problem." In the field of antibiotics preliminary results from the treatment with streptomycin give hope of suppressive action and point the way to further search for similar antibiotics. As consequence of other studies, it was determined that the United States Public Health Service should be responsible for long-range controlled studies of BCG vaccination. Researches have been undertaken regarding non-tuberculous calcifications, particularly those in histoplasmin reactors. The United States Public Health Service and the National Tuberculosis Association cooperate in the education of the public in the entire field of tuberculosis control.—*The Control of Tuberculosis in the Americas*, T. Parran, *Pub. Health Rep.*, June, 1947, 62: 827.—(O. Pinner)

**Chest X-ray Films of Hospital Admissions.**—Because of the finding of many more tuberculous lesions in student nurses than would be expected, a program of taking a chest film on every patient admitted to the Meyer Memorial Hospital, Buffalo, New York, was initiated. Stereoscopic 4x5 inch miniature

films were taken. Over a period of two years the uncorrected figure for unsuspected tuberculosis was found to be 3.7 per cent and when this was corrected by the finding of positive sputum or postmortem examinations it was found to be 1.8 per cent. It is believed that at least 2.5 per cent of all new patients would be proved to have pulmonary tuberculosis by adequate investigation and that those cases with suspicious X-ray findings should be handled as such until proved otherwise.—*Routine Chest Roentgenograms of Hospital Admissions*, G. N. Seatchard & D. O. Duszynski, *Dis. of Chest*, July-August, 1947, 13: 312.—(E. A. Rouff)

**Tuberculosis in Belsen Camp.**—Of 6,000 inmates found at Belsen, 90 per cent were free of cardiac and pulmonary lesions on X-ray examination. Advanced pulmonary tuberculosis was found in 9 per cent, while the number of minimal lesions was small. The findings are interpreted as indicating survival of the most resistant ones.—*Die Schirmbildbefunde von Belsen*, F. Kollbrunner, *Schweiz. Ztschr. f. Tuberk.*, 1947, 4: 118.—(B. Gerstl)

**Tuberculosis among Medical Students.**—Primary tuberculous infection now occurs later than it did at the beginning of this century. This is brought out by the results of skin tests. While five decades ago the cutaneous reaction was positive in an immense majority of 18-year-old individuals, a considerable portion of this age group now shows negative skin tests and remains so beyond 20 and even close to 30 years of age. A follow-up of 1,047 medical students averaging 22 years was made for four to six years. At the start there were 117 (11.35 per cent) negative and 904 positive cases among 883 males and 164 females. The percentage of negative reaction among the females was considerably higher than in the males (15.8 per cent against 10.47 per cent). Nine of the 1,047 students had manifest clinical tuberculosis. Three knew about it, 6 did not. The 904 Pirquet-positive cases could be divided into two groups: 658 (72.8 per cent) with a normal chest film and

246 (27.2 per cent) presenting sequelae of a pulmonary or pleural infection. Cases with negative skin test but revealing lesions on radiography were not encountered. Calcification should be taken as evidence of tuberculosis, except in cases of echinococcus infection. Of the Pirquet-negative cases, primary infection occurred in 34 per cent during the time of observation while only 4.37 per cent of the Pirquet-positive cases showed evidence of reinfection. The reinfections, however, were more severe than the primary lesions. Early treatment resulted in recuperation of 90.9 per cent, allowing these students to continue their courses.—*La tuberculose des étudiants en médecine*, E. Rist, *Schweiz. Ztschr. f. Tuberk.*, 1947, 4: 94.—(E. Oesterlin)

**Rehabilitation.**—Rehabilitation in tuberculosis has been defined as "the restoration of the patient to the fullest physical, mental, social, vocational, and economic usefulness of which he is capable." For reaching this goal case-finding is important. Extensive and prolonged therapy is necessary in advanced cases with their emotional and psychological concomitants which seriously reduce the capacity for work, while early diagnosis will be followed by complete recovery. The process of rehabilitation is important in case-finding; actively employed, cured tuberculous patients testify to the utility of early diagnosis. The type of treatment—collapse therapy or bed-rest—should be chosen with the economic and social circumstances of the patient in mind. Most patients must be almost ready to work when leaving the hospital. Education for a practical employment objective must be started as early as possible under consideration of the individual's limitations, skills, interests and abilities. A program in teaching elementary and advanced subjects is an essential for every institution in which tuberculosis is treated. Occupational therapy has to be related to the patient's actual needs and his preparation for a successful vocational adjustment; the library helps by teaching the use of reading material.

Adjustment to the reality of having tuberculosis and confidence must be brought about by physicians, nurses and other people coming in contact with the patient. Tuberculous patients have greater difficulty than others in finding a happy integration in the life of the community; the author tries to develop interest in the common problems of the hospital community, responsibility and group discipline, by creating a patient council, a patient-operated paper and other social activities. The problems arising from the insecurity prevalent after discharge from the hospital should be anticipated during hospitalization. An understanding physician, with the aid of a public health nurse and a social worker, will help the patient to overcome these difficulties. The Office of Vocational Rehabilitation under the Federal Security Agency has, in coöperation with the States, the responsibility of developing a program of vocational rehabilitation for physically disabled persons, including tuberculous patients. It has funds available for training and education which will lead to a reasonable chance of a patient's becoming employable and for support of the patient during the period of rehabilitation. The costs of rehabilitation are overcompensated for by savings of expenses which, without this procedure, would arise from readmissions, maintenance for the family of a rehospitalized breadwinner, the hospitalization of patients infected by relapsing persons and the consequences of broken families in terms of juvenile delinquency and public dependency.—*The Need for Total Rehabilitation of the Tuberculous*, H. M. Payne, *Nat. M. A.*, May, 1947, 39: 111.—(O. Pinner)

#### Tuberculosis without X-ray Evidence.—

The work for this thesis was started in the Sanatorium Putaendo in 1943 on a series of 46 patients who were clinically inactive but had a positive sputum. Standardized and serialized X-rays films showed, if anything, completely unchanging residual lesions. The majority of these patients had lesions of the hematogenous type. More than half had

bilateral lesions. Pneumothorax and phrenophraxis done in 20 cases did not convert the sputum. In the X-ray films, no changes were observed during a period of three to forty-one months (average thirteen months). The sputa were positive, either on direct examination, culture or gastric lavage. This, of course, is a definite sign of an open lesion in the respiratory tract. Only tomography may detect the presence of small cavities or infiltrations. In case of negative X-ray findings, bronchoscopy and bronchography should be done and, if necessary, repeated. In 10 of the cases, specific lesions in the trachea or main bronchi were found only during bronchoscopy. Four of those also had bronchiectases; 25 cases presented small localized bronchial dilatations which are believed to be the source of the positive sputum. In 5 cases, no lesions responsible for the positive sputum could be found. This is attributed to the insufficiency of present diagnostic methods. As neither rest nor collapse therapy result in a cure, it is suggested to discharge those patients with occasional positive findings but to keep them and their contacts under periodic supervision.—*El problema de tuberculoso pulmonar bacilifero con imagen radiologica de aspecto residual*, Doctor Dissertation, J. Sabbagh Dada, Published by "Relampago", Santiago de Chile, 1945, Pp. 63 with 124 illustrations.—(W. Swienty)

**Regression of Hematogenous Pulmonary Lesions.**—A 23-year-old male, who showed no primary lesions in an earlier chest film, later developed multiple nodular shadows of irregular outline in both lungs. These sometimes were confluent and were interpreted as secondary exudative lesions due to extensive hematogenous dissemination. Over a period of fifteen months the lesions gradually regressed. One year later, the urine was positive for tubercle bacilli and a diagnosis of tuberculous prostatitis was made. Shortly after, a dorso-lumbar spondylitis with cold abscess in the lumbar region was noted. The following year, the patient died of a tuberculous meningitis.—*A propos de la régression*

*de l'image radiologique des lésions micro-nodulaires des poumons*, R. Jeanneret & P. Siegrist, *Schweiz. Ztschr. f. Tuberk.*, 1947, 4: 247.—(E. Oesterlin)

**Constitution and Tuberculosis.**—Constitution has a definite influence on the acquisition and the course of tuberculosis. Of all tuberculous patients in Chile, 47 per cent were mestizoes with a predominantly white component, 25 per cent were real mestizoes, 19 per cent almost pure whites and less than 7 per cent pure whites. Negroes and mulattos gave a very small percentage according to the small number living in Chile. Among the pure whites, the relation between latent and active cases is 1:7, whereas among the mestizoes, it is 1:14. The tendency to localization of the tuberculous process is twice as good in the whites as in the mestizoes. The clinical history of the whites is generally a long one, whereas in mestizoes the disease is very often a fulminating one, although the lesions may be of the same type in both races. Bilateralization is predominant in whites and rare in mestizoes but extrapulmonary localizations are three times as predominant in mestizoes as in whites. Sex is no factor in the severity of the infection. The asthenic type contributes 82.3 per cent of all cases. In this body type, 36.4 per cent show far advanced lesions, whereas of all the rest, only 26 per cent are of the far advanced type. Productive lesions are found in 40 per cent of the asthenics as against 52.1 per cent of the nonasthenic type. All patients of the plethoric type show progressive bilateral lesions. There were 62.3 per cent of the patients who were underweight. The disease was generally more advanced and more progressive in underweight patients than in those with normal weight or those that were overweight. Fifty-three per cent of the patients were up to 23 years of age, 42.3 per cent from 23 to 56 and 4.6 per cent were over 56 years old. In older patients, the course of the disease is more benign.—*Constitucion y tuberculosis*, R. Toro Rojas, *Ap. respir. y tuberc.*, Santiago, January-March, 1947, 12: 63.—(W. Swienty)

**Pyopneumothorax in Primary Tuberculosis.**—This condition is extremely rare. The case described is the second ever to be published in Cuba. A 19-months-old infant was exposed to repeated massive contact and acquired a primary infection. Gastric lavage was positive for acid-fast bacilli. The lesions underwent rapid caseation and ulceration and finally the pleura was perforated. The exudate became a mixed empyema by descending infection. Despite thoracotomy and pleural lavage with tyrothrycin, the patient died. The value of surgical treatment is discussed. There is to-day a greater readiness for immediate surgery as a life-saving intervention, especially if it is done under completely aseptic conditions and bactericidal and bacteriostatic products like penicillin and tyrothricin are being used freely.—*Primoinfeccion tuberculosa a evolucion maligna complicado con pioncunotorax*, R. Valledor, *Rev. cubana de tuberc.*, July-September, 1946, 10: 250.—(W. Swienty)

**Primary and Reinfection Tuberculosis.**—The terms primary and reinfection tuberculosis are inaccurate and should not be used to designate specific anatomical and clinical types. No morphological data support the alleged differences between such lesions. Such differences as have been described may be explained by the time elapsed between the primary attack and reinfection. Reinfection does not necessarily mean a type characterized by little or no node involvement. It may also prove to be the determining cause bringing about a progressive primary type lesion. This has been the case with Negro workers in South African mines, American Negroes and probably to a large extent among Brazilian Negroes and mulattos. The type of lesions in reinfection cases depends on a number of variables, including virulence, dosage of infection, allergic hypersensitiveness and acquired and natural resistance. The rôle of the genetic factor has also of late received recognition. However, all these variables are closely interdependent. When stating that the genetic constitution of the Negro predisposes him to tuberculosis, it is also meant

that tuberculous infection incites in him a higher allergic sensitiveness and a lower immunity than among less susceptible persons. Illustrations of 3 typical cases in 17 to 18-year-old girls are attached to demonstrate the lack of a morphological distinction between primary and reinfection lesions.—*Tuberculose de primo-infecção e de re-infecção*, F. Poppe de Figueiredo, *Rev. brasil. de tuberc.*, November-December, 1946, 15: 465.—(A. A. Moll)

**Artificial Pneumoperitoneum.**—During a pneumoperitoneum refill, an omental vein was punctured, resulting in a fatal hemorrhage. A similar accident occurred in a second case but did not result in a fatality. This complication occurred twice in 3,616 refills in 129 patients.—*A Case of Fatal Peritoneal Hemorrhage Complicating Artificial Pneumoperitoneum*, V. C. Cornwall & W. H. Partridge, *Tubercle*, August, 1947, 28: 164.—(A. G. Cohen)

**Intrapleural Pneumonolysis.**—In 820 operations for section of pleural adhesions, there were 40 cases in which appreciable postoperative bleeding occurred. No cases of hemorrhagic diathesis were involved. There were other cases with slight bleeding (less than 2 ounces). In 20 cases, it was necessary to perform thoracoscopy within a week after onset in order to break up and aspirate blood clots; in 2 other cases thoracoscopy was required in order to stop bleeding. Blood transfusion was needed in 14 cases. Hemothorax was originally regarded as something of a disaster. If not fatal, it led to obliteration of the pneumothorax or to empyema. The artificial pneumothorax suffered no harm in only 6 of the 40 cases. In 18, there was slow creeping out of the lung at the base. In 6 cases, the hemothorax did not start until at least two days postoperatively; in the other 3 cases, it occurred within two days. The source of the blood was in the cannula tract in 9 cases, in the adhesion stump in 4 cases and unknown in 26. Hemothorax is less frequent if pneumonolysis is complete. Empyema occurred in 14 cases. Obliteration

of the pneumothorax space occurred in 10 cases; in many, the cavities remained closed and the sputum negative. From follow-up studies, it was found that the original pessimism was not justified. Nevertheless it is an unwelcome complication. In prevention, careful postoperative handling of the patient is regarded as important. Should bleeding occur, early withdrawal of blood is desirable.—*Haemothorax following Section of Pleural Adhesions*, W. E. D. Moore & J. Watt, *Tubercle*, August, 1947, 28: 161.—(A. G. Cohen)

**Pneumonolysis.**—Indications and technique of Maurer's modification of pneumonolysis are presented in detail. This method combines diathermic coagulation with electrocautery and reduces complications to a minimum. The majority of European authors recommends now to sever adhesions early. Adhesions even if not preventing collapse of the lung should be included because tuberculous foci within and beneath adhesions never heal. Thoracoscopy is the only way to judge extent and operability of adhesions. Thoracoplasty is to be preferred in cases where caustic procedures involve more than usual risk.—*Gegenwärtiger Stand der Thorakokaustik nach der Methode von Maurer*, H. R. Stettbacher, *Schweiz. Ztschr. f. Tuberk.*, 1947, 4: 63.—(B. Gerstl)

**Pneumonolysis.**—A total of 820 operations for section of adhesions was performed on 557 different patients. Upon discharge, the disease was quiescent in 211 cases, much improved in 117 and improved in 121. Complete pneumonolysis was obtained in 235 cases, nearly complete in 90, partial in 239 and slight in 23. The effect was considered good in 276 cases and moderately good in 170. Temperature rises of over 101°F. occurred in 74 cases, not over 101°F. in 113, not over 100°F. in 223 and not over 99°F. in 180. Early pleural effusions were found in 293 cases; only cases in which the fluid reached the dome of the diaphragm were counted. In 125 cases, the fluid disappeared in less than



three weeks. Late effusions were found in 83 cases. In 23, they occurred during the third to eighth week; in 60, they occurred after the eighth week. How many were attributable directly to the operation is uncertain. Many were severe, with a high percentage containing tubercle bacilli and resulting in empyema. Of the 83 cases, 17 lasted less than twelve weeks and 56 lasted longer. In 17 cases, the artificial pneumothorax had to be abandoned and in 13 the pleural space was obliterating. Fourteen of the patients have done well and 39 moderately well. Very few empyemata occurred in thoracoscopy cases in which no adhesions were cut, indicating that these late effusions were attributable to section. Hemothorax occurred in 5 per cent and empyema in 10 per cent of all cases. Eight per cent of the early effusions, 24 per cent of the late effusions and 35 per cent of the hemothoraces became purulent. In a few cases, repeated aspiration resulted in drying up of the fluid, so that pneumothorax could be continued. Lavage with Azoehloramide-T was valuable. When the effusion became purulent, pneumothorax was discontinued and attempts were made to reexpand the lung. If there was extensive previous disease, reexpansion was not attempted; instead, a thoracoplasty was preferred. The cytology of the fluid was no guide to the outcome. Other complications were spontaneous pneumothorax in 15 cases, bronchopleural fistula in 4 cases and air embolism in 2 cases (fatal in one).—*The Complications of Adhesion Section in Pulmonary Tuberculosis*, J. Watt, *Tubercle*, August, 1947, 28: 158.—(A. G. Cohen)

**Endobronchial Tuberculosis and Collapse Therapy.**—Pneumothorax or phrenicectomy in cases complicated by endobronchial tuberculosis may cause irreversible atelectasis. A partial plastic may be successful in cases of collapse involving only the upper lobe. An extensive thoracoplasty should be carried out only if bronchostenosis, resulting from healed endobronchial lesions, prevents reexpansion of the lung. In view of the otherwise poor

prognosis, pneumonectomy may be indicated if the bronchial stenosis causes retention of secretion and bronchiectasis.—*Die Bronchustuberkulose vom Standpunkt des Chirurgen*, A. Brunner, *Schweiz. Ztschr. f. Tuberk.*, 1947, 4: 218.—(B. Gerstl)

**Resection in Tuberculosis.**—The indications for total pneumonectomy in tuberculosis are: the active cavernous type with stenosis of the principal bronchus; hemoptysis due to bronchial dilatation or disseminated pneumonitis; multiple residual cavities after thoracoplasty; tension cavity with extensive homolateral lesions (in preference to cavity drainage); other unilateral conditions in which pneumothorax is not adequate. Lobectomy is indicated for: cavities of a lower lobe which are not influenced by pneumothorax or phrenicectomy; cavities in other lobes which do not respond to collapse therapy, especially in children and adolescents where, by this treatment, a crippling scoliosis can be avoided; open cavity after thoracoplasty; tuberculoma; bronchiectases limited to one lobe. Even very active lesions or lesions in other parts of the lung, as long as they show tendency to regression, are not contraindications. The greatest disadvantage is that, during pulmonary resection, healthy lung tissue must be sacrificed and thus a definite tendency to a lowering of the respiratory function in the not resected segments is created. Complications are: bilateralization in 11 per cent of all operated cases; exacerbation of inactive foci; empyema and ulcerations in the bronchial stump. Adequate pre- and postoperative care tends to diminish these complications. In the opinion of the authors, primary pulmonary resection has its definite place in the surgical treatment of tuberculosis. Three case histories are given.—*Las resecciones pulmonares en tuberculosis en el Hospital Sanatorio "La Esperanza"*, E. Iglesias, S. Caroll del Valle, M. Garcia, A. Sanchez de Fuentes, Jr. & D. Madam, *Rev. cubana de tuberc.*, April-June, 1946, 10: 162.—(W. Suienty)

# TUBERCULOSIS IN EUROPE AFTER THE SECOND WORLD WAR<sup>1</sup>

JOHANNES HOLM<sup>2</sup>

Experience has shown that an increase in tuberculosis follows every war. This was indeed the case after the last World War, and the increase in tuberculosis in Europe to-day is perhaps greater than after any war in the past. It has often been considered natural that this should occur, but only insufficient explanation of the increase has been advanced. Now that we know so much more about tuberculosis than in the old days—now that we have, in particular, a better understanding of its epidemiology—we should be in a good position to seek out the cause of the present increase in the countries of Europe.

What are the causes of this increase in tuberculosis? Without doubt, the most important cause is the greater opportunity for the spread of tubercle bacilli during and since the war. The whole antituberculosis program, which was really quite highly developed in many European countries, became completely disorganized and, with few exceptions, patients with infectious pulmonary tuberculosis were neither isolated nor given medical care.

Early in the war tuberculosis patients in Germany were forced into work. Manpower was needed, and it was therefore proclaimed that no damage to the health of the patient would result from his working. Not even infectious patients were excluded from the labor force. As a consequence, many patients were seriously affected, and the spread of tuberculosis increased considerably in the places of employment. Then again, sanatoria were taken over for barracks in most of the countries occupied by the Germans. It was necessary to evacuate the patients, and they were sent home to live with their families, where the spread of infection was uncontrolled. At the same time, all organized dispensary work stopped.

In Germany and in many other European countries, two things happened that markedly increased the spread of the disease. Air raids damaged a high proportion of the dwellings, especially in the large cities and towns, and this automatically caused a crowding of the population into the remaining buildings. Because of the continual air raids, the population was forced to spend much time in air-raid shelters or bunkers, which were extremely overcrowded; and here, of course, the best opportunities prevailed for the spread of every kind of disease, including tuberculosis.

Even now, many of the increased possibilities for spreading the disease still exist. In many of the towns, and especially in the large cities, houses are damaged to such a degree that living accommodation is one-fifth of what it was before the war. And yet, practically the same number of people are living in these cities, which means, of course, terribly overcrowded conditions. In many places

<sup>1</sup> Presented before a joint session of the Medical and Public Health Sections at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 20, 1947.

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each family has only one room, and in certain areas—especially in Germany—the population has grown because of the influx of refugees. For instance, many millions of refugees still live in Western Germany, having left their homes in Eastern Germany as the Russian army swept westward. Moreover, since the war, great emigrations have taken place from certain areas, which naturally has resulted in enormous additions to the normal population of other areas. In none of these movements of population have measures been taken for tuberculosis control, and thus patients with infectious tuberculosis have been absorbed into the normal population. No wonder that, both during and after the war, greater possibilities than ever before existed for spreading tubercle bacilli.

Even in a normal population, these conditions would be serious and, in populations with lowered resistance, the problem is acute. There are several reasons for this lowered resistance. Perhaps the most important is malnutrition. In many areas of Europe the population has lived on the border of starvation. The malnutrition in Europe is so well known that it is unnecessary to go into much detail, but some factors should be mentioned which have special significance in lowering the resistance to tuberculosis.

Investigations in recent years have shown not only that the number of calories plays a rôle in resistance to the disease, but that certain elements in the diet have special importance, such as animal proteins, certain vitamins (especially vitamin C), and perhaps calcium. As an example of how insufficient the diet has been, I shall mention conditions in Vienna, where the American Forces have made a special analysis of the nutrition problem. In the official report of the American Forces in Vienna, 1946, it is stated that the average consumption of calories per person was less than 1,500 per day, and that the food contained very little animal protein and, for six months, almost no trace of vitamin C. Also, the amount of calcium in the food was less than one-third of what is considered the minimum for normal nutrition. For two years, however, the normal daily ration for the whole of Central Europe has been less than 1,500 calories per person, which is only half of what a normal Dane consumes.

On the whole, nutrition is worse in the large towns, and especially poor in the large cities. In the country, and to some extent in the small towns, the population has a chance of supplementing the ration. But in large cities, such as Vienna and Berlin, which are surrounded by Russian territory that the people are forbidden to enter, there is almost no possibility of obtaining food in addition to the normal ration.

The low standard of everyday hygiene must be mentioned as another factor in the lowered resistance to tuberculosis. In many countries the general hygiene has been set back a hundred years by the war. Facilities for hygiene simply do not exist. In Germany, for instance, soap has the highest price, next to butter, on the black market! Dr. Redeker, one of the leading tuberculosis specialists in Germany, informed me that he considered the spread of tuberculosis to be largely aggravated by the lowered hygiene standards. He stated that in Germany the men ceased to wash themselves a year ago, but that the women are still fighting desperately to keep themselves and their children clean.

As a final factor responsible for the lowered resistance, the psychic pressure under which the population has lived, and is still living, must be mentioned. We must remember that almost everyone throughout a great part of Europe has lost one or more near relations, and that many are living with no knowledge of their families. They have no future to look forward to, and hence their apathy is understandable. This, I am sure, plays a not inconsiderable rôle, even in the physical resistance against disease.

Now, what is the present tuberculosis problem in the European countries? How wide-spread is the disease in Europe to-day, and how great is the increase caused by the war?

It must be stressed at once that there is a vast difference in conditions among the various countries of Europe. It is a great pleasure for me to be able to state that there has been no definite increase in tuberculosis in the Scandinavian countries either during the war or after it. In Sweden an increase in tuberculosis perhaps could not be expected; but Denmark and Norway were occupied by German troops, and especially in Norway conditions were appalling in the last three years of the war, particularly as regards nutrition. Nevertheless, there was no increase in tuberculosis. This was probably because the highly developed tuberculosis program in Norway was functioning even under the most terrible conditions, and perhaps it is necessary to mention that Calmette vaccination was used more in Norway during the last years of the war than ever before.

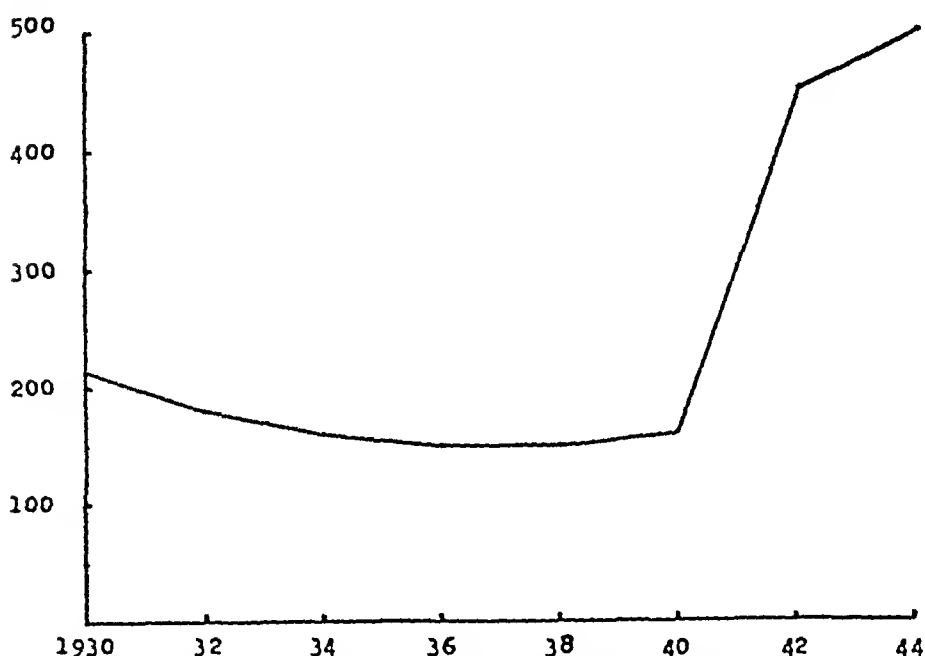
It is very difficult, for several reasons, to obtain reliable statistics concerning tuberculosis in most of the European countries. It must be remembered that in most countries there is still no really well organized tuberculosis program, and that in only a few does a system for notification of tuberculosis function. Even in the countries where such a system exists, the figures obtained are so unreliable that they cannot be compared with pre-war figures. One of the reasons for these conditions is the great shortage of physicians in most countries. In Poland, for instance, almost half the physicians were killed in the war. Again, because of the shortage of physicians, even death certificates are made out, to a large extent, by non-medical people. This, of course, results in inaccurate statistics for tuberculosis mortality, and it is quite understandable that the figures for morbidity are even less reliable.

Furthermore, it is very difficult to obtain figures for the total population on which the statistics must be based. Because of the continuous movement of population, it is almost impossible to estimate how many people have lived in a certain area. The only basis for normal population statistics is the distribution of ration cards. Even this is not too reliable, and it is impossible to obtain the age distribution by this method. It must be remembered that the age distribution in many areas differs widely from the normal. As an example of this: in Vienna in 1946, the age-group 20 to 40 years contained 73 per cent women and only 27 per cent men.

Because of the unreliability of the official statistics, I shall not try to quote figures for all the European countries, but shall only give figures from countries which I have recently visited. Even then, I shall mention statistics for only cer-

tain areas where, from discussions with tuberculosis specialists, I have gained the impression that the figures can be regarded as fairly reliable. The countries I have visited are Germany, Austria, Hungary, Czechoslovakia and Poland. I must say, however, that the increase in tuberculosis is probably worse in other countries, especially Bulgaria, Rumania and Greece.

The time at which the increase in tuberculosis began differed in various countries. In Poland, it came relatively early in the war, as could be expected. The curve for tuberculosis mortality in Warsaw shows that from 1930 to 1940 there was a decrease in tuberculosis from about 200 to about 150 per 100,000 popula-



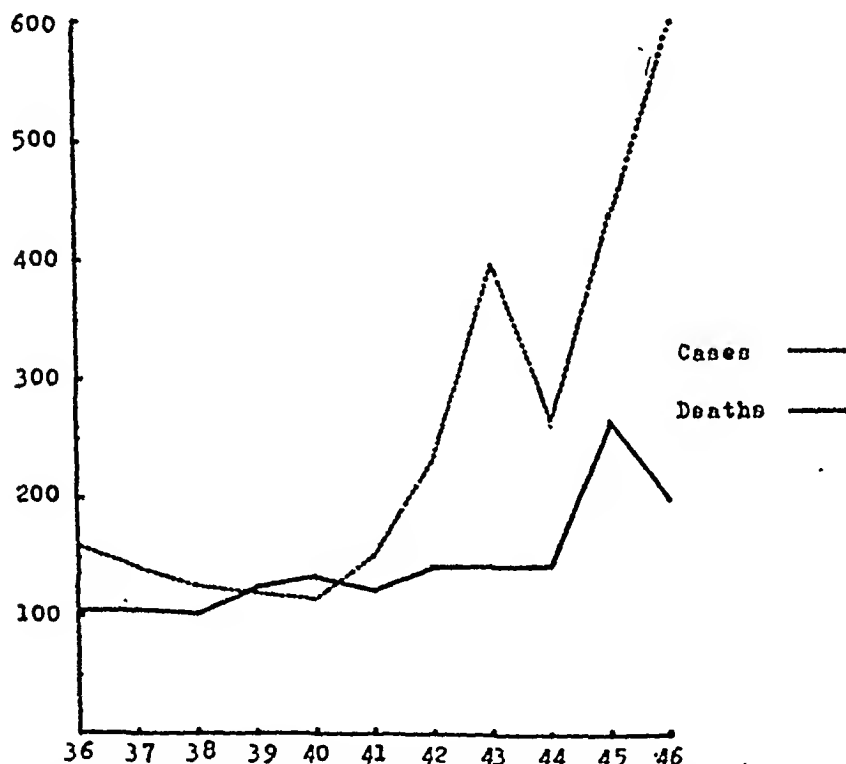
GRAPH 1. Tuberculosis death rates (per 100,000 population) Warsaw, 1930-1944. Official figures obtained from Ministry of Health, Poland.

tion. As early in the war as 1942, the mortality had increased to three times the 1940 figure, and later there was a further, not inconsiderable increase (graph 1).

In Germany and Austria, the increase did not occur until the latter years of the war. Graph 2 shows the mortality and morbidity from tuberculosis in Vienna. By 1945 the mortality had almost doubled. It was lower again the following year. There is a special explanation for the great increase in tuberculosis mortality in 1945. It was the experience of tuberculosis specialists in Vienna that the people who died of tuberculosis that year were those who had had the disease for some time. It must be remembered that conditions in Vienna, particularly in 1945, were terrible, and one would expect these conditions to have affected especially the people with tuberculosis. A high percentage of them simply died off. It will be seen from the curve that there was some increase in the morbidity

from tuberculosis as early as 1940, but the really big increase did not occur until 1944. In 1946 more than four times as many cases were reported as in the years before the war. It can be seen from graph 3, which shows the data month by month, that tuberculosis morbidity in Vienna is increasing to-day. The curve has a very steep upward trend, and it is to be expected that the mortality curve would show the same rise.

In order not to give the impression that it is only in the large cities that tuberculosis increased during and after the war, I shall quote some figures from



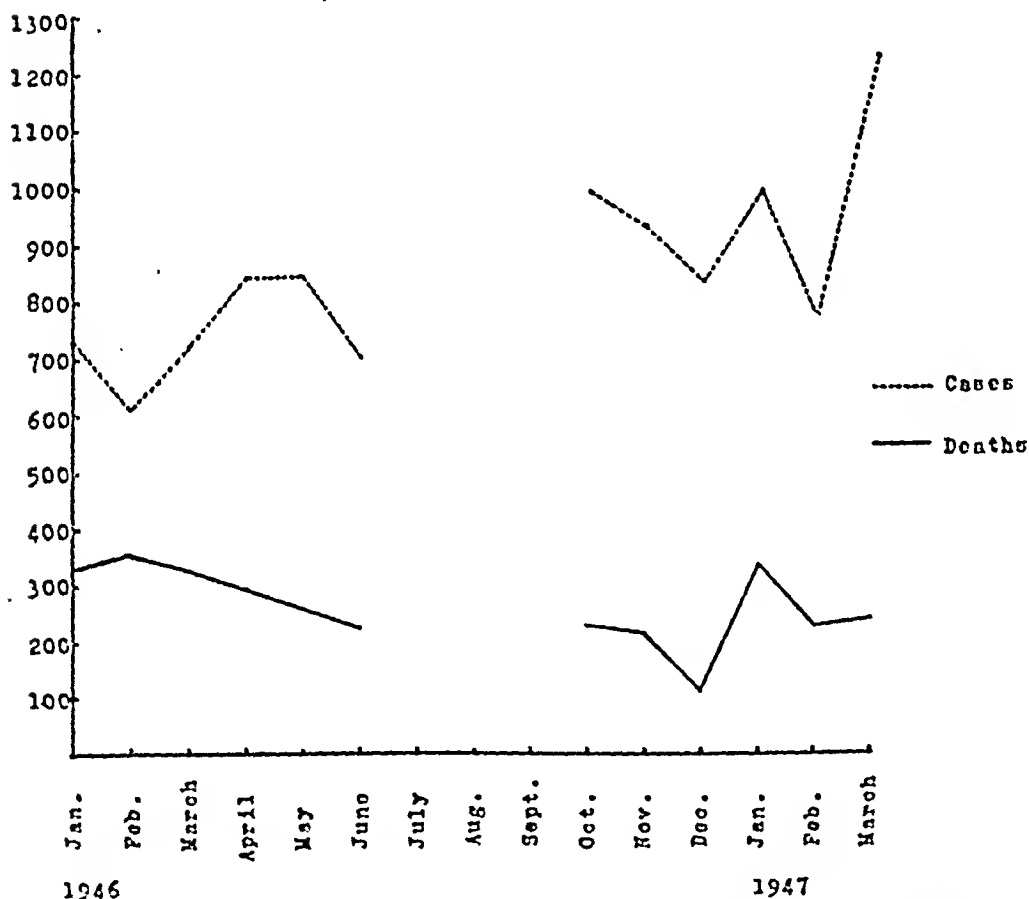
GRAPH 2. Deaths and new-reported cases of pulmonary tuberculosis in Vienna, 1936-1946 (rates per 100,000 population). Statistics obtained from *Magistratisches Amt für Statistik, Vienna* (1945-1946 figures subject to final correction).

Schleswig-Holstein in the northern part of Germany. This is a typical farming district with only a few large towns, but even there a considerable increase in both the morbidity and mortality from tuberculosis is evident (table 1). Only the morbidity and mortality figures are shown, since it has been impossible to obtain reliable statistics for the normal population and, hence, impossible to give the rates per 100,000 inhabitants. On the whole, the population was relatively stable in this area until 1945, but in that year the population almost doubled—from 1.5 to 2.7 million. Even if this is taken into consideration, the number of deaths and the new cases of tuberculosis are several times as high as they were before the war. In Schleswig-Holstein, tuberculosis is still increasing, as may be

TABLE 1

*Number of new cases and deaths of tuberculosis in Schleswig-Holstein, 1939-1946*

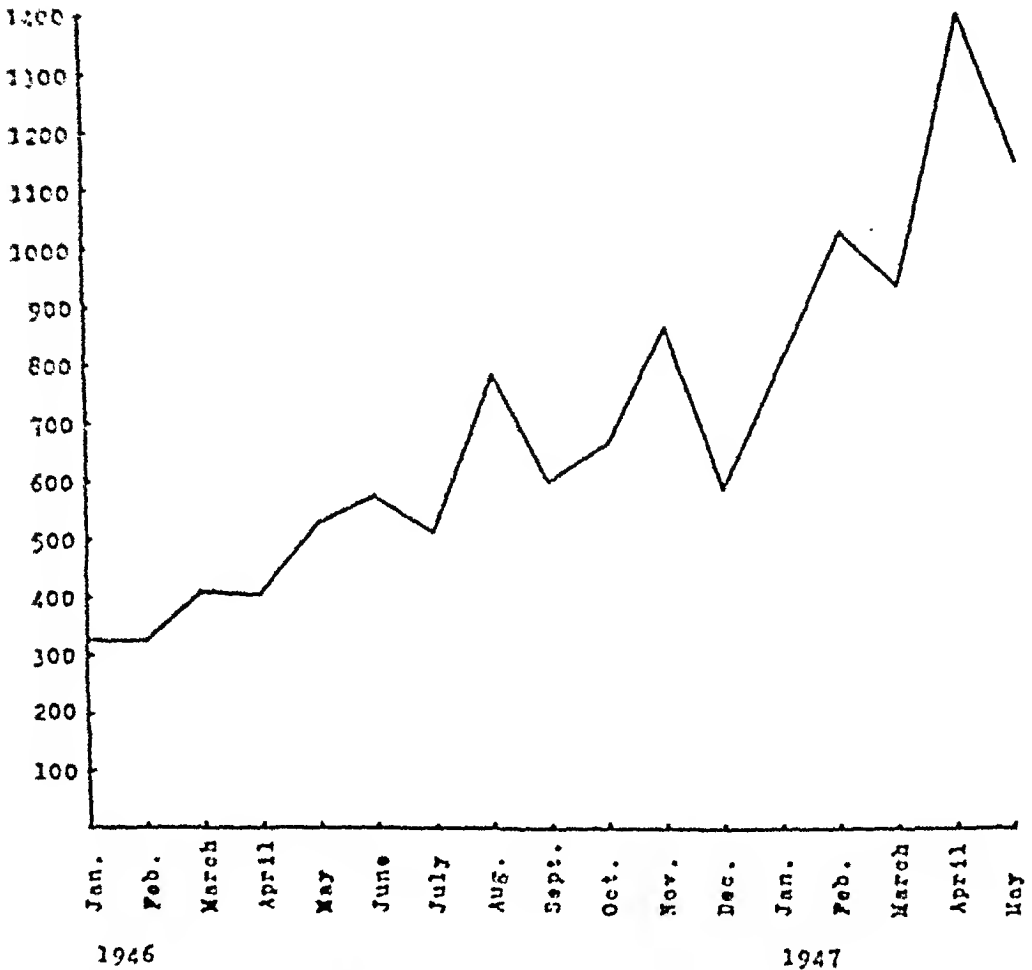
YEAR	CASES	DEATHS
1939	1,252	407
1940	1,242	449
1941	1,516	578
1942	1,818	442
1943	2,414	637
1944	3,191	721
1945	6,034	1,332
1946	6,575	2,754



GRAPH 3. Number of deaths and new-reported cases of pulmonary tuberculosis per month in Vienna, January, 1946 to March, 1947. Statistics obtained from *Magistratisches Amt für Statistik, Vienna*.

seen from graph 4, which shows the number of new cases per month since January, 1946. The curve has a distinct upward trend.

In order to arrive at a detailed explanation of the increase in tuberculosis, it would be necessary to know the age distribution of the cases. As mentioned before, however, this has been impossible to obtain. Nevertheless, it is the general impression of specialists in the various countries that the increase is especially great among children and young adults.



GRAPH 4. Number of cases of tuberculosis reported in Schleswig-Holstein, 1946-1947. Population in Schleswig-Holstein 1946 was 2,790,000.

During my study of the tuberculosis problem in the countries of Europe, the condition that made the deepest impression upon me was the vast number of cases of tuberculous meningitis among children. In some countries tuberculous meningitis among children is almost epidemic. Even the cases of pulmonary tuberculosis among children in these countries are quite different from those we usually see—at any rate in Denmark. In Vienna and Warsaw, I observed, even among small children, many cases of tuberculosis of a typical adult type, with large cavities. There has also been a tremendous increase in extrapulmonary



forms, such as tuberculosis of the bones, joints and kidneys. It has been possible to obtain some figures for Poland that show the increase in tuberculosis among children. In Poland in 1946 the tuberculosis morbidity for all persons was twice the pre-war figure, but for children, four times as many cases were reported as before the war.

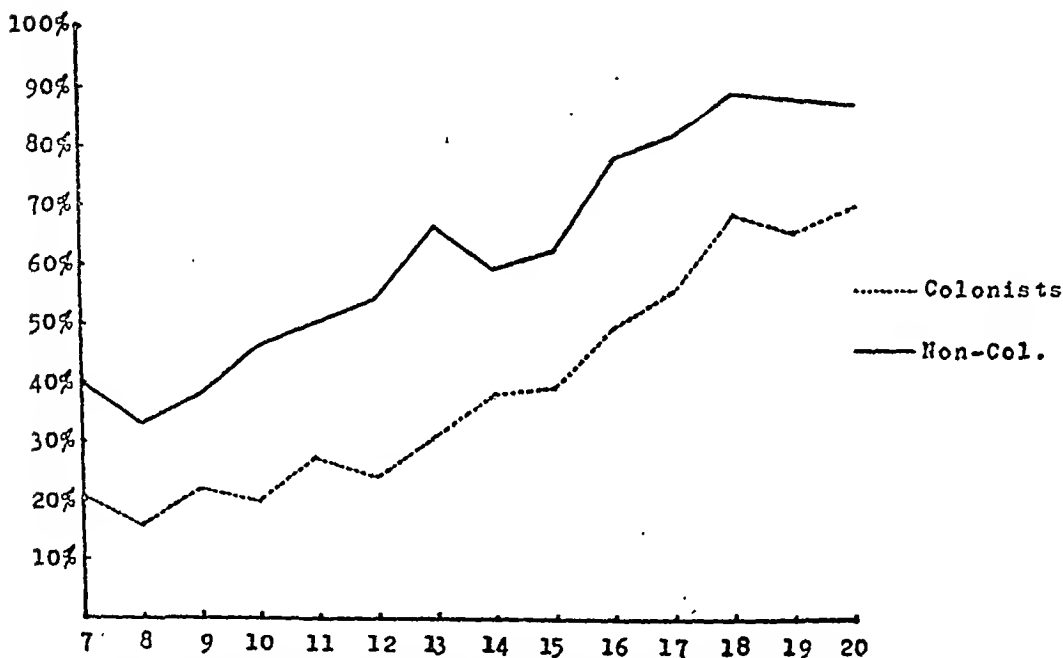
Among adults, the increase is greatest for the young, and particularly for males. From the figures on tuberculosis after the first World War, it is known that the increase was especially high among young adults, but at that time it was mainly the women who were affected. In Berlin in 1946 the mortality from tuberculosis was 302 per 100,000, as against 82 before the war—an increase of more than 350 per cent. At the same time, there were five times as many cases among men as among women, in the age-group 18 to 40 years.

The specially high increase among children and young adults points to the fact that many of the cases are primary tuberculosis. This has been ascertained from the direct experience of tuberculosis specialists in the various countries. No wonder it is so dangerous for young adults to get a primary tuberculous infection under conditions such as those which exist in many European countries to-day! In Denmark, investigations in recent years have shown that, among adults with primary tuberculous infections, 5 per cent contract a progressive tuberculosis. This demonstrates the danger of the so-called natural vaccination. These investigations were made among a population living under good nutritional and social conditions; but under present conditions in many European countries, the percentage contracting progressive disease will certainly be very much higher.

This raises the question of how many of the adults, especially the young adults, are nonreactors to tuberculin and, in particular, were nonreactors before conditions became so bad. Tuberculin tests made before and during the war, on the normal population in Germany for instance, show that the reactor percentage was relatively low in many areas. A tuberculin examination made on the recruits in the German army in 1942 shows that in the 20-year age-group only 60 per cent were reactors. In recent years examinations have shown an increase in this percentage. An examination of school children in Schleswig-Holstein in Germany, made by Doctor Hein, showed that, in 1942-1943, 38 per cent were reactors at the age of 14. An examination made in 1946 by the same doctor among exactly the same groups showed more than 50 per cent reactors at the same age.

It is of course dangerous to have so many nonreactors to tuberculin among young adults under conditions where the possibility of infection is so much increased. After the first World War, the percentage of tuberculin reactors was much higher all over Europe, and practically the whole population was tuberculin-positive at the age of 14. The tremendous increase in tuberculosis after World War II may be explained by the great number of young adults who are nonreactors to tuberculin. When a population living under post-war conditions is heavily exposed to tuberculosis, a great number of primary infections will result, not only among children but among adults as well, and this must cause many cases of primary tuberculosis.

The great movements of population which have taken place with no tuberculosis control have resulted in the people of an area with a low percentage of reactors moving to another area with a high percentage. That this has actually happened has been demonstrated by the examinations carried out by Danish doctors sent to Yugoslavia and Germany by the Danish Red Cross. In Yugoslavia a great number of people from Montenegro, which for many years has had a low incidence of tuberculosis, were sent down to Vrbas in another part of the country (graphs 5 and 6). An examination made in Vrbas showed a great difference between the reaction percentages of the stable population and the colonists. At the same time, it was found that especially among the colonists a great number



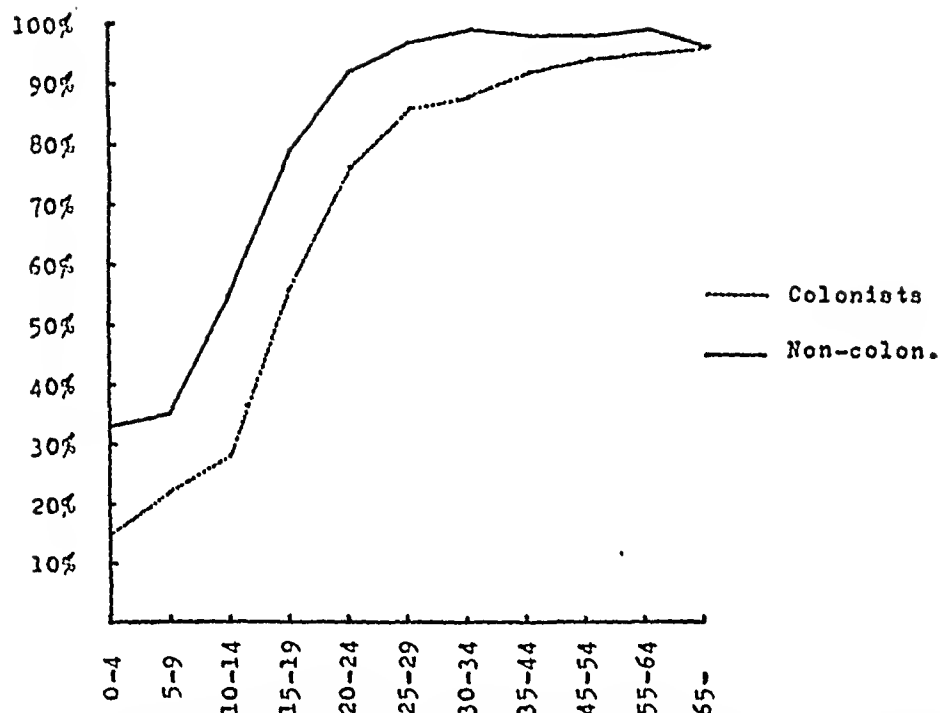
GRAPH 5. Percentage of tuberculin reactors (Mantoux test) in Vrbas, Yugoslavia, 1947, by ages. Tuberculin tests made by the Danish Red Cross.

of typical primary infections and cases of primary tuberculosis occurred, not only among children but also among adults.

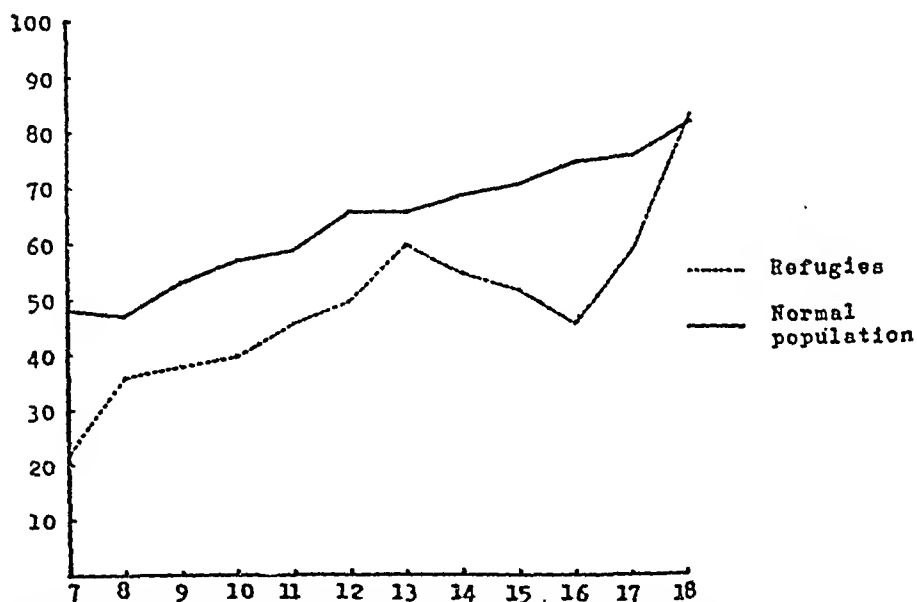
In Schleswig-Holstein, a similar difference was found between the reaction percentages of the stable population and the refugees (graph 7).

Under such conditions, it would be expected that many cases of tuberculosis would occur among the tuberculin-negative persons. We have had the same experience in Denmark, on a small scale. On the island of Bornholm, there has been a very low percentage of reactors for many years. When people from the island went to other parts of Denmark where the infection rate was higher, many of the nonreactors returned with tuberculosis.

An accurate measure of the spread of tuberculosis in a population can only be obtained through mass examination of nonselected groups. An examination car-



GRAPH 6. Percentage of tuberculin reactors (Mantoux test) in Vrbas, Yugoslavia, 1947, by age groups. Tuberculin tests made by the Danish Red Cross.



GRAPH 7. Percentage of tuberculin reactors (Mantoux test) on school-children in Schleswig-Holstein, 1947, by ages.

ried out in Warsaw by the Swedish Red Cross showed that 7 to 8 per cent of the adults had lesions in the lungs suspected of tuberculosis, and that in more than 1.5 per cent the tuberculosis was considered active. Not all of these were examined for tubercle bacilli; and without demonstration of tubercle bacilli the diagnosis is always uncertain; but from groups where examinations for tubercle bacilli were made, it was ascertained that at least 1 per cent of the total number examined discharged tubercle bacilli demonstrable in sputum.

From all this, it is evident that tuberculosis in Europe to-day has spread to an extent greater than at any other period in this century, and that the best opportunities exist for a further spread of the disease. Both the morbidity and mortality curves in many countries still show an upward trend, and this is not to be wondered at. It must be remembered that in most of these countries such tuberculosis programs as do exist are only partly functioning. In many countries there is not only a great shortage of doctors and nurses, but also a catastrophic shortage of all the equipment necessary for a modern campaign against tuberculosis, especially X-ray equipment. Furthermore, there is a tremendous shortage of institutional beds for isolation and treatment of tuberculous patients. A great percentage of sanatoria was destroyed during the war. In Poland, for instance, before the war, there were about 8,000 beds for tuberculosis patients. At the end of the war, there were only about 4,000 left, and these were in sanatoria partly destroyed and stripped of all equipment. In Poland now there are about 12,000 beds, but many more are needed. At least 60,000 beds would be needed there in order to have the bare minimum of one bed for each annual death from tuberculosis; and conditions are just the same in many other countries of Europe.

What can be done to help fight tuberculosis in Europe to-day? It must be stated at once that it is absolutely necessary to arrange for help from the outside.

What is most needed is *leadership*. It must be remembered that a great number of the leading tuberculosis specialists either died during the war or dropped out of action after the war. The reasons for this last fact vary. In Germany leading specialists in the tuberculosis campaign from 1933 to the end of the war were members of the Nazi Party, and it has therefore been difficult for many of them to take an active part in the post-war campaign. In other countries in Europe there has been a change in the political system, and many of the doctors who before the war were holding leading positions are not allowed to hold them now under the new regime. Furthermore, it must be remembered that a great part of Central Europe, including Germany and the German-occupied countries, was cut off from the rest of the world for many years, and therefore had no possibility of obtaining information on what was happening in the medical world from 1938 to the end of the war. Even now it is almost impossible for them to get medical literature from other countries. The effect of this is considerable. Within the specialty, in the last decade, there has been a great evolution called the "tuberculosis campaign," and this is new and unknown to practically all the physicians in the countries I have mentioned. At the same time, the physicians there are very eager to obtain as much information as possible from abroad. I have experienced this personally, through the lectures I have given in Europe.

A relief action is necessary; but how shall this action be organized?

In Denmark we have given this question deep consideration and have tried to arrive at a practical solution. I shall briefly mention the tuberculosis relief action organized from Denmark through the Danish Red Cross—especially because it illustrates that something can be done, and describes the program for relief to countries where the tuberculosis situation may lead to national tragedy.

This action has two aims: (1) the sending out of direct help to different countries and (2) the inviting of foreign physicians to Denmark to observe and study a modern tuberculosis program.

It is of great importance that the physicians who are going to take over the actual tuberculosis program in the different countries have an actual opportunity to see a tuberculosis program working on modern principles. Therefore, doctors from many countries in Europe have been invited to Denmark, to enable them to have an education in the different specialties within the tuberculosis program, including (1) tuberculosis dispensary work, (2) tuberculosis epidemiology, (3) bacteriology of tuberculosis and (4) therapy of tuberculosis. In connection with this action, we try to furnish the leading tuberculosis specialists with as much as possible of the tuberculosis literature published in recent years.

The aim of the direct relief action is, first of all, a large-scale Calmette vaccination, to some degree combined with diagnosis of the really infectious cases of tuberculosis. With a prevalence of tuberculosis like that in Europe to-day, it might seem hopeless to give any help. But much can be done. Tuberculosis is in an epidemic stage in many countries, and it is therefore the aim of our work to combat that epidemic along the same lines as those used for epidemics of other diseases, such as diphtheria and typhoid fever. The actual experience in the different countries, and the reliable statistics available, point to primary tuberculosis as the cause of the present great increase of the disease in Europe. Now, we know from much experience in the Scandinavian countries that these cases of primary tuberculosis can, to a large extent, be prevented by Calmette vaccination. Therefore, our first aim is to check, by Calmette vaccination, the great inflow of new cases. We have sent teams of Danish physicians and nurses to different countries in order to conduct mass tuberculin surveys and vaccination of all nonreactors to tuberculin among whole population groups. Such a team starts in a certain area and demonstrates how the mass examinations and vaccinations should be organized and carried out. At the same time, physicians from the countries concerned are taught the technique of tuberculin testing and vaccination. After the first demonstration, mixed teams are set up, consisting of Danish and local personnel; and it is our hope that later the local doctors and nurses will take over practically all the work. One team, consisting of a physician and two nurses, can tuberculin-test and vaccinate the nonreactors at a rate of 2,000 persons a day. Two Danish teams working in Warsaw have tuberculin-tested and vaccinated all the school-children in that city and have started vaccination of young adults. Altogether, there are four Danish teams, composed of five physicians and ten nurses, working in Poland. We are acting along the same

lines in the British Zones of Germany and Hungary, and are just about to start in the American Zones of Germany, Austria and Czechoslovakia.

It is our opinion that the most important part of the campaign is the vaccination—that it is of less importance to start a case-finding survey, especially one that uses a very fine diagnosis. Through X-ray examination in many countries, we would find that 1 to 2 per cent of the population had tuberculosis, but as there are no possibilities for isolation and treatment, this would be of very little help in fighting the disease. The Danish relief action, therefore, is not planned primarily as an X-ray survey; but, in order to diagnose the worst sources of infection in the population, the tuberculin test is combined with an examination of sputum for all adults with productive cough. Persons with productive cough and many tubercle bacilli in sputum must first of all be isolated in order to cut down the infection rate. Because of the shortage of food, it has been difficult in many countries to keep the infectious patients in tuberculosis sanatoria. Patients in institutions cannot obtain extra food from the black market! Therefore a number of sanatoria are provided with Danish food through the Danish Red Cross.

In addition to operations in the countries mentioned, the Danish Red Cross has worked for six months in Yugoslavia, where a tuberculosis dispensary, after Danish principles, was established as a demonstration, and the next step in the relief action will be to start such dispensaries in other countries as well. Negotiations are in progress for beginning the same type of work in Rumania, Italy and perhaps other countries.

It has been an advantage that this relief action has started from Denmark, because Denmark is a small country and permission for the work was perhaps more easily obtained than it might have been by the bigger nations. On the other hand, however, the resources of Denmark are limited, and it would therefore be most desirable to obtain help from other countries, for instance from the U. S. A.

It has been difficult in Denmark to obtain all the equipment needed for the teams already working in the various countries of Europe, and we have been most grateful to receive some help from the American Red Cross. Our greatest problem is to get such items as cars, instruments, X-ray equipment and paper.

It is not sufficient to send equipment to the different countries without teaching their tuberculosis workers how to use it correctly. I learned this from my recent visit to Prague. There I saw 15 complete sets of quite modern American apparatus for mass photofluorography, which had been sent to Czechoslovakia from the United States as a gift. Only one of these had been in use, and that for only a short time. The Czechs simply did not know how to use the apparatus or how it should be applied in a practical way in the tuberculosis campaign. This stresses the necessity for leadership and direct instruction.

In many places equipment for the tuberculosis institutions is needed. It is possible to get the buildings for sanatoria, and perhaps the beds, but bedding and other equipment cannot be obtained. Practically everywhere, there is a shortage of instruments for treatment, such as pneumothorax needles and thorascopes.

For the National Tuberculosis Association in this country, there is a great work to be undertaken in assisting voluntary agencies in Europe to get started. Send out some of your best men as observers to see the situation in Europe to-day, and you will be convinced that help is needed. Your leadership will be invaluable.

#### CONCLUSIONS

The tuberculosis situation in Europe to-day is serious, even very serious, but it is not hopeless!

As mentioned several times, it is necessary to bring outside help to many of the European countries. The means of providing this help exist. The main thing is to organize the help in the right way, by starting a real international coöperative effort for the fight against tuberculosis.

We used to say, "No home is safe from tuberculosis until every home is safe." Modern transportation facilitates the spreading of disease from one country to another, and therefore no nation can completely eradicate tuberculosis until it is eradicated throughout the world. By taking an active part in the international efforts to control the disease, we protect our own home and country. And thus we will not only progress in the campaign against tuberculosis, but will also contribute essentially to a better understanding among nations—an understanding badly needed in the world to-day.

#### CONCLUSIONES

##### *Tuberculosis en Europa*

La situación tuberculosa en Europa hoy día es grave, y podemos decir, hasta muy grave, pero no desesperada!

Como se ha dicho varias veces, es necesario llevar ayuda de afuera a muchos países de Europa. Ya existen los medios de facilitar esta ayuda. Lo principal es organizarla con acierto, iniciando una verdadera empresa cooperativa internacional para la lucha contra la tuberculosis.

Solíamos decir: "No hay hogar a salvo de la tuberculosis hasta que todos los hogares estén salvos." Los modernos medios de transporte facilitan la propagación de la enfermedad de un país a otro, por lo cual ningún país puede erradicar completamente la tuberculosis sino después que esté erradicada en todo el mundo. Participando activamente en los esfuerzos internacionales contra la dolencia, protegemos nuestros propios hogares y países. No sólo avanzaremos así en la lucha antituberculosa sino que contribuiremos fundamentalmente a una comprensión mejor entre las naciones: comprensión esta harto necesaria en el mundo hoy día.

# TUBERCULOSIS IN SOUTH AMERICA<sup>1</sup>

HÉCTOR ORREGO PUELMA<sup>2</sup>

## SOCIAL AND ECONOMIC PANORAMA

To understand the tuberculosis problem in South America without an understanding of present-day socio-economic conditions and racial factors in the various countries is an impossibility. We, therefore, wish to commence by sketching briefly the salient social, economic and geographical features of the Continent.

The twenty Latin-American Republics have a total population of 130,000,000 inhabitants, spread over approximately 20 million square kilometers. Thus a population similar in number to that of the United States occupies two and a half times the latter's territory, suggesting a lower level of population density in South America than in the United States. However, due to the vast stretches of jungle, mountain, desert and other uninhabited land in South America, the population is not as thinly spread as these figures might seem to suggest. The low population density is apparent rather than real; and it is necessary to use other and more accurate measures of population concentration, such as the number of persons per room or per bed, if we wish to obtain a true picture of population conditions as they concern tuberculosis and the possibility of spread of infection. No detailed statistics are available, but the few inquiries that have been made indicate that there is much more crowding, that is, many more people per room and per bed in South America than in the United States. If we add to this "crowding" of people together, the low standard of living of the majority of the people, it seems reasonable to conclude that South Americans are much more exposed to contagious air-borne diseases than North Americans.

Sayé points out that in the last ten years the highest mortality rates known have been registered on the Pacific Coast of South America and that, although the demographic displacements that have taken place here are not comparable with those of Europe during the second half of the 19th Century, the tubercularization waves have been produced by population shifts to the cities and, in general, by an intensification of industrial, agricultural and commercial activities.

A person crossing the United States from San Francisco to New York, by way of Chicago, would find that both the standard of living and the mixture of races were fairly similar throughout all stages of his journey. In Latin America the same traveller would receive quite a different impression.

From the racial point of view, Latin America can be divided into three large geographical areas. The countries making up the tropical areas are inhabited by Indians, Negroes and the descendants of Spaniards, all of whom have mixed,

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but in varying proportions. The subtropical zone is quite similar, except that the Negro element is much smaller. (At the time of the slave trade the Negro's muscular strength was not held in great demand by the plantation owners of this region.) In the temperate and cold regions the Negro factor is completely absent from the racial mixture, leaving only the Spanish and Indian elements. Since, at the time of colonization, the Spanish women did not accompany the Conquistadores due to the vast distances and the constant fighting, the men mixed freely with the Indians. The result is an Indian-Spanish mixture, that is rather homogenous.

From the economic point of view, and again using the geographical groupings of tropical, subtropical and temperate, we find that the countries comprising the tropical group have one common characteristic: they are essentially one-industry countries, devoted either to agricultural or mineral production. Their cities, therefore, serve merely as centres where manufactured objects from abroad are exchanged for the agricultural and mineral products of the interior. They have no industries that can properly be called indigenous, and since "market places," which is what they really are, do not call for large concentrated populations, the cities remain small and the great mass of the respective populations live scattered throughout the interior of the respective countries.

The subtropical zone includes countries very similar to those of the tropical regions, in that they have one- or two-industry economies. However, the raw materials are processed to some degree; there is a sort of semi-manufacture of products before exportation. And with the factories have come larger cities and a more clear-cut division between urban and rural populations. What is even more important, is the fact that in this zone urban population is increasing markedly, while in the tropical zone there is little evidence of change.

In the temperate zone, that is, in the extreme south of the Continent, industries have grown up and agricultural crops are diversified. This, of course, has led to an active commercial interchange with other countries and the necessity for large cities of one or two million people. This temperate zone is much more comparable to the United States than either of the two regions mentioned before.

Of course, the quality and types of housing and nutrition differ greatly from one zone to another. Unfortunately, no numerical index can be used to show this difference, since not only are feeding habits quite diverse but the purchasing value of the money in the various countries is quite unstable and differs widely from one place to another. We, therefore, prefer to use the study made by the Latin-American Worker's Federation (*Confederación de Obreros Latino-Americanos*) of the amount of meat and milk that a worker can obtain for an hour of labor. Not all countries are included, but the study gives examples that are quite typical of each zone. It also demonstrates, quite well, the great difference in the standard of living between one zone and another. (Table 1.)

Accepting as an established fact, first that there are differences in racial susceptibility to tuberculosis; second, that its course is influenced by the standard

of living; and third, that the probabilities of getting infected are conditioned by the population density, we should still have to recognize the fact that these three factors have differing importance in the various zones and compensate for one another to a certain extent.

In the tropical and subtropical zones the presence of two highly susceptible racial groups, the Negro and the Indian, and of a low standard of living, which results inevitably from the type of national economy discussed before, causes a condition highly favorable to a rapid spread of the disease. On the other hand, the fact that the majority of the people are engaged in agricultural or other rural activities, resulting in low population density, diminishes the possibilities of contagion and gives tuberculosis a local character. That is, while in certain cities of this zone the level of infection is quite high, the probability of this level

TABLE 1

*Purchasing value of one hour's wages for milk and meat in Latin-American countries, compared with the United States*

ZONE	MILK IN LITRES	MEAT IN KGS.
<b>Tropical</b>		
Ecuador.....	1	0.2
Bolivia.....	1	0.2
<b>Subtropical</b>		
Mexico.....	2	0.4
Colombia.....	3	0.4
Cuba.....	2	
<b>Temperate</b>		
Argentina.....	5	1.5
Uruguay.....	5	2.0
Chile.....	2.5	0.6
United States.....	10	2.0

becoming general is slight, considering the changes of the economy of the different zones.

In the temperate and cold zones of the south, the Indian racial strain, strongly reinforced by European blood, is more resistant to tuberculosis and a higher standard of living prevails than in the other two zones. However, there are offsetting features. Although industrialization is backward as compared to the United States, it has been taking place and cities have grown rapidly in recent years. Serious overcrowding has resulted, facilitating the contagious process of the disease. All the characteristics of a stage of maximum infection are present.

We think, therefore, that, while one part of Latin-America is undergoing a phase of increasing infection, the other presents evidence of an already established maximum infection, with the exception of a few cities where there has

been a great deal of European immigration. In these latter, tuberculosis seems to be declining.

The statistical data extant support this interpretation. Unfortunately, there are no central organizations which compile statistical data and we know that the information published by individual countries varies as to its reliability. The countries which are economically advanced issue information of good quality. However, those which are more backward present only incomplete figures and even these are not always reliable.

TABLE 2

*The degree of industrialization and agricultural work according to tropical, subtropical and temperate zones in Latin-American countries, compared with the United States*

ZONE	COUNTRY	PER CENT AGRICULTURAL WORK	PER CENT INDUSTRIAL WORK
Tropical or one- industry	Bolivia	88.7	1.1
	El Salvador	73	5.1
	Ecuador	—	—
	Honduras	72.4	7.7
	Haiti	—	—
	Rep. Dominicana	84.3	6.2
	Paraguay	—	—
	Venezuela	84.7	5.6
Subtropical or in- termediate	Brazil	59.4	6.7
	Colombia	62	16.9
	Guatemala	71.1	12.5
	Mexico	70.0	10.4
	Peru	62.5	17.2
Temperate or in- dustrial	Argentina	42.4	16
	Chile	34.7	19.6
	Uruguay	45	13.1
	United States	18	28.9

Data for three countries are not available and Panama is deliberately excluded because the Canal Zone creates conditions that are quite different from Latin-America in general.

Subject to the above limitations, we have prepared a table showing the percentage of the population engaged in industrial and in agricultural work for most of the countries on the Continent. In table 2 we have classified the countries according to the three zones previously mentioned, paying little attention to climatic factors, which for our purposes has little importance, but instead measuring each country against the yardstick of whether or not it belongs to a zone in which the one-industry economy predominates.

#### APPRAISAL OF TUBERCULOSIS IN SOUTH AMERICA

With this brief summary of the socio-economic conditions of South America as a background, we wish now to present such data as are available about the status of tuberculosis in the various countries.

We cannot give general figures for the Continent as a whole, nor for every country, since reliable statistics are often missing. Such data as are available often refer only to small groups within a given country and relate to greatly varying periods of time.

Therefore, in trying to comply with the request of the National Tuberculosis Association to report on tuberculosis in South America and to do so with something approximating standardized statistics, we sent a questionnaire to our colleagues in the various countries, asking them to report on the following topics for their respective nations: morbidity and mortality rates; incidence; results of mass surveys; amount of BCG vaccination done and any results observed; distribution of tuberculosis by age, sex, economic condition and location (urban or rural); and recent legislative measures concerned with tuberculosis, as well as other details.

Information was received from Argentina, Brazil, Paraguay, Venezuela, Ecuador, Uruguay and Peru. Information covering other countries was assembled in large part from the Proceedings of the Fifth Pan-American Congress on Tuberculosis, held in Buenos Aires in 1940, and from Dr. Luis Sayé's book entitled *Doctrina y Práctica de la Profilaxis de la Tuberculosis*. Many other sources were consulted and much valuable aid was given by Professor Raúl Vaccarezza of Buenos Aires, Professor Boettner of Asunción, Drs. Armando Sarno and Fernando Gomez of Montevideo, Dr. Isaac Pardo of Venezuela, Dr. Jorge Higgins of Guayaquil, Dr. Klinge of Peru, Dr. Reginaldo Fernandez of Brazil and Drs. Benjamin Viel and Herman Romero of the School of Public Health in Chile. We would like, at this point, to express our sincere appreciation to all these men. Without their help, this work would have been impossible.

Let us see what partial data of recent date we have been able to collect:

*Argentina:* The country is 3,650 kilometers in length and 1,700 kilometers in width. Its surface area covers approximately 2,987,655 square kilometers. The population in the 1937 census was 13,320,641.

National data on morbidity and mortality for the last ten years are not available. However, on the basis of such scattered local reports as have been published, we calculate that the general mortality rate for the country is 111.7 per 10,000 and the death rate for tuberculosis 10.13 for 10,000.

There were 148,841 deaths registered in Buenos Aires for the year of 1941. Of this number, 133,040 were certified by a physician and, of these latter, 13,507, or 9 per cent, were due to tuberculosis.

It is interesting to note in what relation tuberculosis stands to other causes of death. In the same year of 1941, first place was occupied by cardiac cases, 10.60 per cent; the second by cancer, 10.06 per cent; and tuberculosis was third, with 9 per cent of all deaths. The remaining causes of death varied between 6.61 and 2.90 per cent.

Also in 1941, the Argentinian Tuberculosis League X-rayed 160,000 apparently healthy persons, most of them industrial workers, and found 3 to 3.5 per cent with apparently active lesions. Examinations carried on among university students by Professor Vaccarezza gave the following figures for apparent active tuberculosis: men, 0.84 per cent; women, 0.74 per cent.

In general, in the country as a whole, Professor Vaccarezza says that he has not found any significant difference in mortality curves by age between the two sexes. For both he finds that the peak mortality is reached around 30 years of age. In Buenos Aires there is a slight difference. Men have a higher mortality than women and the peak is reached around 40 years of age.

Regarding BCG vaccination, the following information is available: by 1945, Raimondi and Urquijo had vaccinated 120,000 new-born children and 2,150 in the preschool age group. In addition, the Argentinian Tuberculosis League had vaccinated over 20,000 persons, mostly new-born infants. No complete study of the results of the vaccinations has been published, but we have some partial reports which indicate that greater resistance is evidenced by those who have received the vaccine than by those who have not.

In the legislative field, we cannot report that any important steps have been taken in regard to tuberculosis. In general, tuberculous patients receive the same social security benefits that other groups of sick people in the population receive. Better provided for are certain groups of public and private employees who belong to mutual organizations. Some private organizations have developed interesting plans in several cities and have obtained official backing.

In evaluating statistics we must not forget that in the population of Buenos Aires there is a high concentration of European elements or of descendants of Europeans, and that consequently the figures for this city differ widely from those for the rest of the country. We quote from Professor Sayago of Córdoba who says:

"It is easy to verify that the curve of tuberculosis mortality in the Argentine Republic is quite dissimilar in different provinces and cities. While in some, tuberculosis is declining, in others it maintains a high level and, finally, in still others the mortality is increasing. Among army privates tested with tuberculin there are 57.1 per cent with positive reactions among those who come from rural areas, as against 80.3 per cent among those who come from the capital city."

Sayago also reports that there are great differences between different provinces, for example, in the provinces of San Luis and Santiago del Estero there are 49 deaths per 100,000 inhabitants, while in Jujuy and Salta there are 328 deaths per 100,000. Such tremendous differences can be explained by the fact that the population density in Argentina is very low (4.4 inhabitants per square kilometer) and the majority of the population is engaged in agricultural pursuits in these low density zones where spread of infection is limited. When these same people, with their Indian racial background, group together in the large cities, as they have been doing recently, the mortality figures shoot up since they have little or no resistance.

*Paraguay:* The country has an area of 452,872 square kilometers, and, though there has not been a census for quite some time, the population can be estimated at a million and a half people, of which 126,915 live in Asunción.

Professor Boettner has given us epidemiological data covering some 60 per cent of the population, or about 780,000 people. He has warned us that all data concerning Paraguay, with the exception of Asunción are quite unreliable,

not only because of the deficiency of dependable statistical analysis and collection, but also because there is a lack of medical diagnosis in ascertaining causes of deaths.

With this in mind, we present, in table 3, figures on tuberculosis mortality per 100,000 people for the years 1940 to 1945.

In 1945 to 1946, 37,749 people were tuberculin-tested in Asunción. The Mantoux method was used and 95.61 per cent reactors were found. In rural areas, Doctor Buzarquis tested 1,570 persons, using only one injection of 0.1 mg. OT. He found 15.15 per cent reactors. This considerable difference in the percentage of reactors between the capital city and rural areas leads to some interesting observations on the state of tuberculosis in South America as a whole. It points to the existence of an ascending infection level that reaches massive proportions when people leave rural zones of low population density and congregate in urban centres. Since Argentina and Paraguay have a common

TABLE 3  
*Annual tuberculosis mortality rate in Paraguay, and separately  
in Asunción, per 100,000 from 1940 to 1945*

YEAR	ASUNCIÓN	REST OF THE COUNTRY
1940	143	28
1941	184	30
1942	144	31
1943	152	45
1944	162	47
1945	145	46

frontier, but quite different socio-economic conditions, we thought it interesting to consider the one immediately after the other and deliberately put them in this order.

Also, in connection with mass surveys, in a study of supposedly healthy segments of the population and of known contacts to open cases made in Asunción in 1946, 1.32 per cent of active tuberculosis was found. This percentage was, in turn, broken down as follows:

Primary infection.....	0.44 per cent
Minimal reinfection lesions.....	0.22 per cent
Advanced reinfection lesions.....	0.66 per cent

Among causes of death in Asunción in 1940 to 1941, tuberculosis ranked first and was followed by bronchopneumonia or pneumonia, and then by gastrointestinal diseases, especially diarrhea in children under 2 years of age.

The peak mortality for tuberculosis occurs between the ages of 20 and 40 and is higher in women than in men.

BCG vaccination is practiced only in Asunción, where the multipuncture method of Rosenthal is used. To date, 5,000 persons have been vaccinated by this method, but results cannot yet be judged.

Regarding legislative measures, the state offers some protection to workers who contract tuberculosis through its compulsory *Ley de Previsión Social*. By its provisions, a person with confirmed tuberculosis receives his regular salary for a six-month period, which time may be extended to a year and a half if it can be demonstrated that there is a chance for a cure. If, after the six-month period, the case is believed incurable, the patient is entitled to apply for a life-time disability pension.

Government employees who contract tuberculosis or leprosy do not come under this act. There is a special law giving them compensation, which may not be less than 50 per cent of their regular salary, for at least two years. If a cure has not been effected by this time, they are entitled to retire on the same basis as a person who has served out his full term of years in the Government Service.

To receive benefits under either of the above laws, a person must have taken a medical examination which includes a tuberculin test and an X-ray film.

It should be pointed out that private organizations in Paraguay are also doing very valuable work. However, there is a grave deficiency in the number of beds available for tuberculosis.

*Uruguay:* With its 186,926 square kilometers it had, according to the official census of 1937, 2,093,333 inhabitants and a density of 11.20 persons per square kilometer, which is the highest in Latin-America. There is a strong current of European immigration. Uruguay is probably the only South American nation in which tuberculosis is positively decreasing throughout the country as a whole.

The average mortality rates for tuberculosis for the entire country are as follows:

1930 to 1934, per 100,000 inhabitants,	134.2
1935 to 1939, per 100,000 inhabitants,	112.6
1940 to 1943, per 100,000 inhabitants,	109.3

The peak mortality is reached between 15 and 30 years of age.

A survey made of known contacts to open cases of tuberculosis revealed 12.35 per cent of active cases. In the population at large, a similar survey revealed the following information:

Industrial workers.....	3.2 per cent active tuberculosis
Army privates.....	2.1 per cent active tuberculosis
Bank employees.....	3.3 per cent active tuberculosis
Grammar school children.....	1.7 per cent active tuberculosis

As we have seen in other countries, the morbidity varies according to zone, whether urban or rural. The same holds true even in Uruguay, where the highest population density in South America is found. The infection levels in Uruguay, as measured by tuberculin-testing surveys, are as follows:

*Northern zone:* Living conditions are substandard, there is undernourishment and overcrowding.

Tuberculin reactors—adults.....	62.2 per cent
Tuberculin reactors—children.....	25.2 per cent

*South-western zone:* Living conditions are normal, nutrition good and there are no large urban centres close by.

Tuberculin reactors—adults.....	45	per cent
Tuberculin reactors—children.....	26	per cent

*South-eastern zone:* Living conditions mediocre, nutrition deficient, and constant movement between this zone and large urban centres.

Tuberculin reactors—adults.....	60	per cent
Tuberculin reactors—children.....	37.1	per cent

*Central zone:* Living conditions mediocre, nutrition deficient, completely rural.

Tuberculin reactors—adults.....	78	per cent
Tuberculin reactors—children.....	67	per cent

*City of Montevideo:*

Tuberculin reactors—adults.....	81	per cent
Tuberculin reactors—children.....	63	per cent
Tuberculin reactors—infants.....	9.7	per cent

BCG vaccination has been actively carried on, and in 1945 there were 125,739 persons vaccinated, of which, 15,700 were under adequate control. According to Professor Fernando Gomez, it can be said that among the vaccinated the morbidity and mortality is one-fourth of that found in the control group.

The control program in Uruguay has been developed very satisfactorily through the following organizations: the Anti-Tuberculosis Prevention and Aid Service of the Department of Public Health; the Department of Public Education, which maintains a Tuberculosis Institute, complete with dispensary, lying-in hospital for tuberculous women and a vaccination centre—all in the medical school; the War Department, which maintains centres where epidemiological studies are made and which provides a certain number of beds; the Municipality of Montevideo, which provides health examinations and X-ray examinations for domestic servants, food handlers and people who work in the transportation industry; and, finally, the Institute of Inter-American Affairs, which has aided the Department of Public Health in building and equipping three health centres in the most important cities of the country.

All in all, with its 1943 tuberculosis mortality of 2,631 and its 2,600 beds, Uruguay has its tuberculosis problem under control to a degree not equalled anywhere else in South America. Moreover, at the present time there are 1,900 more beds under construction, which will bring the total number to 4,500.

As regards financial aid for tuberculous patients, in 1934 a law was passed granting three years of rest with full salary to any Government employee who contracted tuberculosis. In 1945 a National Permanent Fund for the Fight against Tuberculosis was created, with contributions coming both from the state and from private sources. The Fund is to be used exclusively for needy families of tuberculous patients, either hospitalized or confined to bed in their own homes.

There are many other activities that we have not mentioned which are carried on by the Anti-Tuberculosis Prevention and Aid Service of the Department of



Public Health, such as child preventoria, rehabilitation centres, etc. All in all, Uruguay has one of the most complete and interesting tuberculosis programs in South America.

We wish to thank Professor Fernando Gomez who has the Chair of Tuberculosis in Montevideo and Dr. Armando Sarno, *Director del Servicio de Asistencia y Preservación Anti-Tuberculosa*, for the great aid they have given us in sending us very complete data for their country.

*Ecuador:* With an area of 816,414 square kilometers, the country has approximately three million inhabitants. According to Dr. Jorge Higgins, who has given us the information for this section, national statistics are incomplete and defective. Only since 1942, he says, have any reliable demographic studies been made. For this reason, Doctor Higgins has limited his information almost exclusively to Guayaquil, where he lives and does excellent work.

In 1946, Guayaquil had 216,615 inhabitants and in 1945 its tuberculosis mortality was 416.5 per 100,000.

The antituberculosis dispensary in Guayaquil has tuberculin-tested about 10,000 people and found 84.3 per cent reactors.

In the last two years, considerable work has been done with BCG vaccination in Guayaquil. Higgins has become so enthusiastic about the tentative results of the program that to-day he is vaccinating all babies born in the maternity hospitals and all nonreactors that come to the Mother and Child Centres.

In Quito vaccinations were begun in 1940, and by 1946, 4,000 children had been vaccinated. At first oral and subcutaneous routes were tried but at present the Rosenthal technique is used. Some reports on the results in Quito have been published by Dr. Luis Andrade, which we feel are of interest in spite of the fact that they are not complete and give figures on general infant mortality rather than on specific tuberculosis mortality. The percentages refer to the one to 3 year age group. The total mortality was 9 per cent in vaccinated and 32 per cent in nonvaccinated.

At the present time, two big centres of epidemiological research, one in Quito and the other in Guayaquil, are being completed. Beds are being provided in both cities and the Public Health Department is putting into effect a comprehensive five-year plan that should give impetus to the tuberculosis campaign in Ecuador.

*Peru:* The population of the country is 6,500,000 and it has an area of 1,358,000 square kilometers.

According to the information which Dr. Leonidas Klinge obtained for us from the Tuberculosis Department of the Public Health Service, the country is going through a period of massive infection, characterized by a high tuberculosis mortality. There are large numbers of reactors at all ages, with an especially high percentage in the first two years of life, and a large number of cases both clinical and nonclinical, active and progressive. (Table 4.)

Tuberculin-testing in Lima dispensaries revealed 30 per cent reactors in the age group from birth to 2, 50 per cent in the age group 2 to 16 and 85 per cent at ages 16 to 60.

Mass surveys of supposedly healthy segments of the population have given results of more than 3 per cent active nonclinical tuberculosis.

As to extent, 30 per cent were minimal, 40 per cent moderately advanced and 30 per cent far advanced.

In the same survey a study was made of housing conditions, salaries and nutrition of the tuberculous patients found. Housing conditions were good in 10 per cent, fair in 50 per cent and bad in 32 per cent. In terms of real wages, 25 per cent had a sufficient income, while 75 per cent had an insufficient income. Only 20 per cent had good nutrition, 50 per cent fair nutrition and 30 per cent were classified as having bad nutrition.

In 1941, the National Anti-Tuberculosis Service was created. Its stated purposes were to do preventive work and also to provide medical care for patients. The Service directs and coördinates all activities in the tuberculosis program. It has also begun to collect and centralize tuberculosis statistics. Moreover, the Service is working indirectly towards tuberculosis control by

TABLE 4

*Tuberculosis mortality per 100,000 in various Peruvian cities in 1945*

CITIES	TUBERCULOSIS MORTALITY RATES	CITIES	TUBERCULOSIS MORTALITY RATES
Tacna	625	Chiclayo	269
Callao	483	Arequipa	418
Mollendo	449	Cuzco	264
Pisco	348	Puno	244
Lima	357		

attempting to improve housing, diets and wages. It also brings health and sanitary education to the people.

At present the means with which the Service has to work are limited, especially as regards the treatment phase of their program. However, there is a plan under way which will provide for 6,470 beds to be distributed in general hospitals, regional sanatoria and preventoria for children, scattered throughout the country. In addition to this, 28 dispensaries will be constructed in various parts of the nation.

BCG vaccination has been carried on since 1933 by the Tuberculosis Department of the Public Health Service, but we have been unable to secure any data concerning the results of the program.

*Mexico:* In spite of the fact that this study was to be limited to South America, we wish to take advantage of our contacts with Dr. Ismael Cosío Villegas, Professor of Tuberculosis in Mexico, to include some valuable information on tuberculosis in his country. We feel that this information will help to round out the report.

Mexico's 1930 census reported that the population was 16,552,722. According to official estimates, by 1939 the number had risen to 19,478,791. Of this

latter number it is estimated that one-third lives in urban areas and the rest in rural areas.

It is interesting to note that, in the general budget of \$445,265,943.78 for 1939, \$16,500,000 were allotted for Public Health work.

Regarding morbidity and mortality, Doctor Cosío Villegas estimates that in 1939 there were some 300,000 cases of tuberculosis and some 30,000 deaths caused by tuberculosis in the country.

A tuberculin-testing program carried out among school children in Mexico City revealed 49 per cent reactors. The majority of the children were around 12 years of age.

A mass survey, using photofluorography, carried out among policemen, workers applying for health certificates and university students, resulted in the finding of 1.39 per cent of active cases. All in all, the survey covered 250,000 people.

The main work of the control program is carried on by a Department of the Ministry of Public Health and Medical Assistance, which has its own funds and which carries on direct programs of treatment and also does indirect control work through such organizations as the School of Public Health, Nutrition and Hygiene and Sanitary Engineering. The Department runs seven tuberculosis dispensaries in Mexico City and thirty more in other parts of the country. It has at its disposal about 1,350 beds, the majority of which are in the Federal Capital and the rest in other principal cities. At present three more 300-bed sanatoria are being constructed.

There are several preventoria for children and a system of foster-homes for children is also used as a protective measure.

BCG vaccination is being carried on with some intensity but no results are available.

It is interesting to note that in a five-year period the sale of antituberculosis stamps has produced \$6,500,000.

Mass surveys are being constantly carried on for the purpose of making epidemiological studies in two permanent centres where 4 x 5" film is used and in two mobile units where the 35 mm. method is practiced.

Up-to-date data for the remaining South American countries are not available, in spite of the fact that we solicited information immediately upon receiving the invitation to make this study. To use the material published in the various medical journals and especially that given in the Proceedings of the last Pan-American Congresses of Tuberculosis would lengthen this study enormously, without particularly changing the total picture for Latin-America that we have tried to give. These are our reasons for omitting many countries of general importance. However, before presenting our conclusions we want to speak briefly about Brazil and Venezuela and then consider in somewhat detailed form the situation in our own country, Chile.

*Brazil:* Brazil occupies almost half of the South American Continent. It covers 8,611,857 square kilometers and has 45,000,000 inhabitants.

In spite of the fact that tuberculosis mortality is very different in different regions of the country—there are agricultural regions of low density, areas which have recently been industrialized and urban areas of long standing—an average death rate of 250 per 100,000 inhabitants for the country as a whole can be postulated. This figure also takes into account the differences in racial groups in Brazil: Negro, Mulatto and white.

In their interesting book *Roentgenfotografia*, Manoel de Abreu and Aloysio de Paula present certain information which we wish to quote.

In 1940 the Thoracic Centres of Rio de Janeiro X-rayed 12,000 Municipal employees, candidates for jobs and patients in the hospitals and Municipal Clinics who came from diverse social groups. They found 2.5 per cent active cases. On this basis, Abreu and de Paula estimate that there are about 50,000 people with active tuberculosis in Rio de Janeiro.

In the cases making up the 2.5 per cent in the survey, 1.60 per cent were moderate or far advanced with cavities. An additional 5 per cent in the survey had apparently inactive reinfection type tuberculosis.

As regards the presence of clinical symptoms in the cases uncovered by the survey, there was a proportion of one person with symptoms for every 10 without. Among the patients with cavities, for every 4 who were cognizant of their symptoms there were 31 who had no idea that they were ill.

The type of lesion seen was usually exudative, especially in the 20 to 30-year age group.

In the Brazilian contribution to the Fifth Pan-American Congress on Tuberculosis, held in 1940, Abreu and de Paula point out that figures on tuberculin-testing are very incomplete from a national point of view. However, such results as are available indicate a very high percentage of reactors—over 90 per cent among adults in large cities. As contrasted to this, they refer to a rural town, Jacana in the province of Sao Paulo, where reactors only reached 53.1 per cent and the distribution by ages was as follows:

Up to 3 years.....	11.1 per cent
Preschool children.....	21 per cent
School children.....	30 per cent
Young adults.....	66.4 per cent
Adults between 26 and 65.....	80.1 per cent

After this paper was already written, we received some interesting information about the tuberculosis situation in Brazil from Dr. Reginaldo Fernandez, President of the Tuberculosis Society of Rio de Janeiro. The information he presents on BCG vaccination and the Brazilian Anti-Tuberculosis Organization is as follows: BCG vaccination was begun in 1927 by the Brazilian Anti-Tuberculosis League. By 1944 they had vaccinated in Rio de Janeiro 161,663 new-born infants, of whom 25.57 per cent were followed-up. Vaccinations done in other parts of Brazil raised the total number of vaccinated to approximately 350,000.

Tuberculosis control activities are centered about the National Tuberculosis Service whose main offices are in Rio de Janeiro and which has branches in all

principal states of the country. It deals with prevention of the disease, and with the orientation, coördination and financing of public and private tuberculosis institutions. To date the service has built 21 hospital-sanatoria, one for each state, 55 dispensaries and 13 tuberculosis centres where tuberculin-testing is done. At present the service is constructing special tuberculosis pavilions in the general hospitals of the country.

*Venezuela:* The country's area measures 912,050 square kilometers. The present population is estimated at a little over four million. According to a survey made in 1937, the racial composition of the country was as follows:

Indian-Negro-white mixture.....	85 per cent
Indian.....	10 per cent
White.....	5 per cent

As in the case of Doctor Fernandez, the information on Venezuela sent us by Dr. Isaac Pardo of Caracas arrived too late to be included in this report. We, therefore, are using the statistics which Doctor Pardo presented to the Fifth Pan-American Congress on Tuberculosis in 1940.

In urban centres the average tuberculosis mortality is 321 per 100,000 inhabitants. Throughout the country as a whole, and depending upon the locality, mortality rates vary between 210 and 470 per 100,000. In localities where the incidence is high, tuberculosis accounts for as much as 23.16 per cent of the total mortality.

Epidemiological surveys made in Caracas and in rural areas among supposedly healthy population elements gave the following percentages of active cases:

Urban population.....	2.43
Semirural population.....	1.52
Rural population.....	1.02 to 2.2
Indian population.....	0.98
Population in petroleum areas.....	1.51

According to age, the number of active cases is high in infants. It diminishes in the 10 to 19-year-old group and goes up again from this point to reach a peak at 30 years of age.

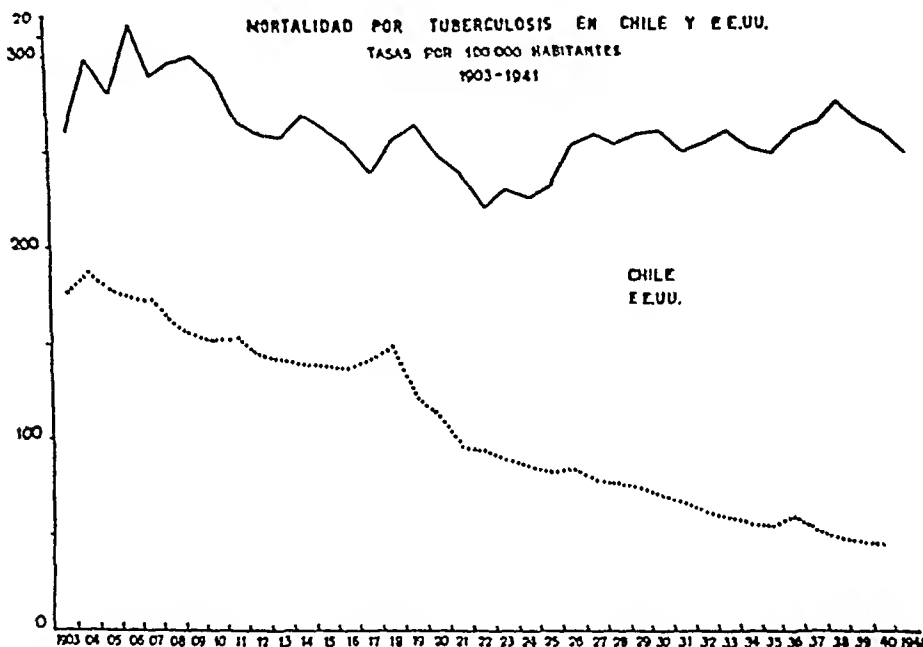
In tuberculin-testing surveys made in urban areas, over 20 per cent of newborn infants were reactors. By 14 years of age, the percentage went up to 51 and in persons over 14, it reached 83.2 per cent. In rural areas, infection is much lower and may be broken down as follows:

Rural population.....	27.3 per cent
Indian population.....	25.9 per cent
Petroleum industrial area up to 14 years .....	40.6 per cent
after 14 years .....	75.1 per cent

We may deduce from these figures that, as in the rest of South America, tuberculosis has two fundamental aspects. In rural or semirural areas of slight population density, where the inhabitants come into contact with urban centres, it is in an ascending phase; in the urban centres themselves and in industrial areas it is epidemic and of massive proportions.

As Doctor Pardo pointed out, one of the important features responsible for the spreading of infection, which is often overlooked, is the frequency with which bovine tuberculosis is found in animals stabled either within or close to urban centres. He says that it is especially prevalent in imported herds.

*Chile:* Chile is a long strip of land, lying between the Cordillera of the Andes and the Pacific Ocean. Its width varies from 170 to 300 kilometers and its length is 4,222 kilometers. In area it covers 741,767 square kilometers and its population is 5,400,000. Almost one-fifth of this entire population lives in the province of Santiago and the capital city itself has around 1,000,000 inhabitants, excluding surrounding towns.



GRAPH 1. Tuberculosis mortality rate per 100,000 in Chile and in the U. S. A. from 1903 to 1941.

Between 1903 and 1946 the tuberculosis death rate of 260 per 100,000 has remained fairly constant, as shown in graph 1. The rates according to age groups are presented in graph 2. Deaths from tuberculosis account for 11.9 per cent of the total mortality. The actual figure is 15,000 annual tuberculosis deaths. In the age group of 15 to 50, the most productive years for the individual, tuberculosis accounts for 32.4 per cent of all deaths. These figures are national averages and vary considerably from zone to zone. In agricultural areas of low population density, the mortality is as low as 100 per 100,000 inhabitants; in a few exceptional urban centres it goes as high as 400 per 100,000 inhabitants.

Morbidity rates for Chile can be determined with a good deal of exactitude. This is due to the fact that general statistics are quite reliable in this country

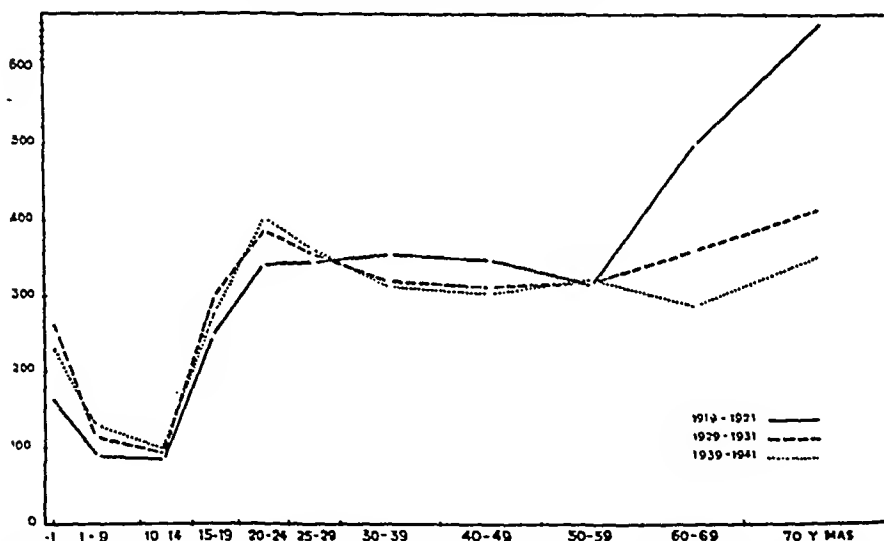
and also because, since 1937, the preventive medicine law, which calls for obligatory health examinations of all workers for the purpose of discovering cases of tuberculosis, syphilis or cardiovascular diseases, has been in force.

Between 1938 and 1943, 600,000 workers of both sexes and 83,000 domestic workers were examined. The results are very useful in establishing morbidity rates in Chile.

In a group of 25,566 employees who were examined, we found active tuberculosis in 3.32 per cent of men and 3.81 per cent of women. In a group of 19,197 workers in the city of Santiago who were taking their regular health examination, we found 3.6 per cent of active tuberculosis (see table 5).

One of the most favorable results of the obligatory health examinations has

MORTALIDAD POR TUBERCULOSIS Y EDAD EN CHILE  
TASAS POR 100 000 HABITANTES  
PERIODOS 1919-1921, 1929-1931 y 1939-1941



GRAPH 2. Average annual tuberculosis mortality rates per 100,000 in Chile for three periods: 1919 to 1921, 1929 to 1931 and 1939 to 1941.

been the complete modification of the type of tuberculosis we see and treat nowadays. While in the out-patient departments of our hospitals we encounter over 50 per cent of the cases in an advanced state of the disease, among the people who come spontaneously or who are screened in the regular health examinations, 38.6 per cent of the cases are minimal and 42.5 per cent are moderately advanced. The remaining percentage is composed of inactive reinfection type cases and of advanced cases.

Investigations made among 3,420 students in the 8 to 15-year-old group, all of them residents of a poor neighborhood in Santiago, 70, or 2 per cent, had active tuberculosis (table 5). Of the 70 cases, 69 per cent had only primary lesions.

According to figures prepared by Doctor Viel in which he used the usual statistical basis, we can estimate that there are 7.4 active cases of tuberculosis

for each annual tuberculosis death, which brings the total number of active cases of tuberculosis in Santiago to 26,665.

As regards morbidity in urban areas, tuberculin-testing reveals almost 100 per cent reactors in the adult population. In school children where investigations are made quite frequently throughout the country and with more or less

TABLE 5  
*Tuberculosis morbidity in Santiago, Chile*  
Survey of 1942 (rate by hundred)

AGE IN YEARS	STUDENTS, GRAMMAR AND HIGH SCHOOL	EMPLOYEES	WORKERS
- 8	2.3	—	—
9-10	1.8	—	—
11-12	1.5	—	—
13-14	2.5	—	—
15-19	3.9	4.1	3.7
20-29	—	4.8	4.1
30-39	—	2.9	3.1
40-49	—	2.2	2.7
50+	—	0.8	2.3
Total.....	2.0	3.5	3.6
Number examined	3,420	25,566	19,197

TABLE 6  
*Number and percentage of tuberculin reactors among  
children of poor families in Santiago, by ages*

AGE IN YEARS	NUMBER EXAMINED	TUBERCULIN REACTORS	
		Number	Per cent
7 to 8	752	450	59.8
9 to 10	1,065	749	70.3
11 to 12	1,017	756	74.3
13 to 14	510	394	77.2
15 to 16	76	57	75.0
Total.....	3,420	2,406	70.3

the same results, we find the figures presented in table 6; they specifically relate to children of poor families from Santiago.

Under our direction, Dr. Alfredo L. Bravo surveyed a small group of country people quite isolated from urban centres and found only 30.2 per cent reactors, which seems to indicate that there are rural zones in Chile relatively free from tuberculosis, as contrasted to highly infected urban areas.

As regards surveys made of contacts to open cases, we have the studies made by Doctors Raddatz and Fernandez who also worked under our direction in the Hospital del Salvador. Among families of tuberculous patients in the hospital



of all ages, they found 17.1 per cent of active cases. Most of the group examined belong to an economically modest or poor social group. Of those under 15 years of age, the percentage of active cases rose to 21.9 per cent.

Viel made a similar survey of contacts to tuberculous patients who belong to a higher social and economic class, namely, civil servants and private employees. In this group, he found 11.1 per cent of active tuberculosis.

We are short of beds in Chile. With an annual mortality of at least 15,000, we have only 3,600 beds distributed among general hospitals, special hospitals and sanatoria. These are scattered throughout the country.

The tuberculosis control program is directed by the Workmen's Insurance Fund (*Caja ó Instituto de Previsión*) and by the Free Social Assistance Bureau (*Beneficencia y Asistencia Social*). Both of these organizations maintain clinics in all important cities of the country.

As we mentioned before, since 1937 there has been in effect the preventive medicine law, written by the then Minister of Health, Dr. Eduardo Cruz Coke, which made health examinations obligatory for all applicants for work and which further provided for an annual examination of workers. The law also deals with compensation and provides that tuberculous patients who are considered curable are to be given a bed or ambulatory treatment by the insurance organization to which they belong and that during the time of cure they are to receive their full salaries.

Before 1937 the Workmen's Obligatory Insurance Corporation (*Caja de Seguro Obligatorio*) which was financed chiefly by employers, then by the worker and finally by the State, could not handle the tuberculosis problem in a satisfactory way, due to the multiplicity of obligations which this Corporation had, such as general medical care and disability and old age pension. The new law provides for a contribution on the part of the employer of 1 per cent of the monthly salary of each employee, plus 2.5 per cent of the gross income received by the various Government Insurance Institutions, to finance the tuberculosis control program.

The results of the new law have quickly become evident. The opportunity for prompt diagnosis and treatment has permitted us to obtain cures between 68 to 72 per cent using the usual therapeutic methods, as against the 30 to 40 per cent that previously obtained with cases that came looking spontaneously for treatment.

Naturally, the new law has not solved the tuberculosis problem in Chile. Moreover, it has its disadvantages. It has created a new and privileged class of curable patients whose economic and therapeutic problems are solved for them. However, the benefits of the law are not available to advanced cases which continue disseminating the disease day after day. These advanced cases cannot even find a bed since a high proportion is occupied by the minimal and moderately advanced clients of the various insurance funds. Also, destitute people are absolutely outside of the preventive medicine law, since only workers come under its protection.

Since 1930, there has been a special Chair of Tuberculosis in the Medical

School. In that same year the Chilean Tuberculosis Society was created. Through its initiative the official classification of the National Tuberculosis Association was adopted in Chile three years ago.

At the present time among Public Health Authorities there is a tendency to unify and centralize all activities in the tuberculosis control program and to devote large sums of money to increase the number of beds now available. In this connection, we wish to point to the valuable aid of the Department of Inter-American Affairs which has just given the Social Assistance Bureau a new and completely equipped 500-bed hospital. It has aptly been named Trudeau in homage to the great American visionary who introduced the sanatorium treatment in this Continent.

#### CONCLUSIONS

1. South America is undergoing an epidemic stage of tuberculosis. In sparsely populated areas the infection level is rising, while in the few crowded urban areas, where there are large groups of Europeans or their descendants, it has begun to decline and an endemic phase has begun.

2. By and large, national statistics are lacking for South America and the data that are available refer only to small areas or groups. There is also a lack of standard statistical methods, preventing the compiling of reliable conclusions.

3. There is a lack of means and resources absolutely necessary for the successful prosecution of the fight against tuberculosis in South America.

4. Social and economic protection is insufficient.

5. It would be desirable and of great aid if a Pan-American Conference on Tuberculosis were held to prepare a uniform system of collecting and classifying statistical information. This would allow us to speak in a common language and to understand one another better.

#### CONCLUSIONES

##### *Tuberculosis en Sud-América*

1. La América del Sur se encuentra en el período epidémico de la tuberculosis. En las zonas poco pobladas el coeficiente de infección va en aumento, en tanto que en las pocas zonas urbanas hacinadas donde hay numerosos grupos de personas de natalidad o de ascendencia europeas, ha comenzado a bajar y se ha iniciado la fase endémica.

2. En conjunto, no hay estadísticas nacionales para Sud-América, y las disponibles sólo comprenden pequeñas zonas o grupos. También faltan técnicas estadísticas depuradas, lo cual impide la compilación de conclusiones fidedignas.

3. Para la lucha con éxito contra la tuberculosis en Sud-América hacen falta los medios y recursos absolutamente necesarios.

4. La actual protección social y económica es insuficiente.

5. Convendría y ayudaría mucho la celebración de una Conferencia Panamericana de Tuberculosis que elaborara un sistema uniforme para la colecta y clasificación de las informaciones estadísticas. Esto nos capacitaría para hablar el mismo lenguaje y entendernos así mejor.

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# THE TUBERCULOSIS PROBLEM IN THE PHILIPPINES<sup>1</sup>

The Rôle of the Philippine Tuberculosis Society and Other Agencies and the Present Postwar Organization

MIGUEL CANIZARES<sup>2</sup>

The paramount health and socio-economic problem of gigantic proportions in the new-born Republic of the Philippines is tuberculosis. Now, in a so-called era of peace, tuberculosis kills at the rate of four lives every hour round the clock. Due to it alone, the state loses one and a half billion dollars a year. From the moment the first bomb fell on Pearl Harbor, two wars were unleashed on the Philippines—one, fought with shell, shrapnel and other known infernal implements of death; the other, in which hunger, wartime living conditions, parasitic infestation and moral and physical tension had to be borne, like a cross, so that subsequent invasion by disease could step in with the utmost ease.

Prewar tuberculosis death rate among Filipinos was 230 per 100,000, five times the 1945 rate for the U. S. Now this death rate is certainly higher. Where there are at least 500,000 cases of tuberculosis among the 18,000,000 population to-day, there are not more than a total of 1,200 institutional beds now available throughout the Philippines for this disease.

The Philippines has a total area about half the size of Texas. In population, its 18,000,000 inhabitants equal the combined populations of New Jersey and New York states.

To New Jersey's four million people, at least 4,203 beds (1942) for tuberculosis are available. In the whole Philippines, with a death rate five times as high, not more than 1,200 such beds can be found. Even before the war, this figure has never been exceeded.

In the Philippines, tuberculosis has headed the list of deaths for decades. Not even malaria can topple it from its pedestal. At war's outbreak, field surveys in 1940 placed moribidity at 6.22 per cent, or 1,119,600 suspect tuberculosis cases. If half of these cases did not survive the war and if no new cases have cropped up meanwhile, at least 500,000 cases are probably still alive to-day. That figure is the minimum that can be arrived at.

Why is this so? What local conditions obtain which tend to make the disease so prevalent and the campaign against it so limited in the Philippines?

Two organizations, which, just before the war, had some sort of mutual understanding, are concerned with antituberculosis activities—a voluntary agency, the Philippine Tuberculosis Society, and the government outfit, which is called the Tuberculosis Control Section under the Health Bureau. The Philippine Tuberculosis Society was affiliated before the war with the National Tuberculosis

<sup>1</sup> Presented before a joint session of the Medical and Public Health Sections at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 20, 1947.

<sup>2</sup> Managing Director of the Philippine Tuberculosis Society, and Medical Director, Quezon Institute, Quezon City, Philippine Islands.

Association and *L'Union Internationale Contre la Tuberculose*. There was an arrangement that the Philippine Health Bureau unit would take care of health statistics and case-finding in field surveys, while the Philippine Tuberculosis Society was to attend to the home and institutional management of cases. The educational work was jointly undertaken by both agencies. To this effect, the Society operated 4 provincial tuberculosis pavilions, 14 dispensary clinics and a central sanatorium, known as the Quezon Institute. On the other hand, the Health Bureau ran a dispensary in Manila, 150 hospital beds for advanced cases and mobile X-ray units for field surveys. These combined agencies examined by fluoroscopy and film a total of 510,843 persons in 1940, or approximately 2.8 per cent of the population.

#### A BIT OF HISTORY

The Philippine Tuberculosis Society was founded in 1910 by a small group of civic-minded citizens. Initially it ran two small clinics in the slum districts of Manila, but gradually its activities expanded until it was able to open a sanatorium in the outskirts of Manila in 1918. The sanatorium at first consisted of a few nipa huts or ramshackles. Year by year new additions were built until, in 1935, there were some 27 cottages and huts. A diagnostic X-ray unit was acquired in 1927, and, in 1929, 17 patients were under pneumothorax therapy. Two years later, phrenic nerve operations and thoracoplasty were introduced in the Islands. Collapse therapy found such wide acceptance that at war's outbreak the Quezon Institute alone had 1,547 pneumothorax patients. Intrapleural pneumonolysis was introduced in 1937. The Philippine Tuberculosis Society and the Quezon Institute started sending members of its staff abroad, especially to the United States, for advanced training.

The sanatorium operated by the Philippine Tuberculosis Society was renamed the Quezon Institute in 1938 after its sponsor, the late Manuel L. Quezon, who later died at Saranac Lake. It may be stated here that the late President Quezon was as interested in tuberculosis as the late President Roosevelt was in infantile paralysis. He it was who sparked the antituberculosis campaign in the Philippines. Under Quezon's administration the sweepstakes law took effect, most of the proceeds of which were set aside for use in the campaign against tuberculosis, besides proceeds from Christmas Seals sales.

Since 1938 the activities of the Philippine Tuberculosis Society steadily expanded. Dispensary clinics and pavilions were opened in populous areas of the Islands. The wooden and nipa structures of the sanatorium gave way to modern concrete buildings with enough room to house 1,400 patients. A planigraph unit was operating from 1939 to the outbreak of the war; clinical and research laboratories and a medical library were founded; an orthopedic service was established; a powerful G. E. apparatus with a miniature 4 x 5" X-ray unit was acquired in \$940; and a scientific publication was issued semi-annually containing the results of researches by the staff. Since 1938, it has begun training physicians sent by the Tuberculosis Control Section of the Health Bureau in tuberculosis work for a minimum period of two years. Undergraduate medical students from three

local medical colleges and nurses from schools of nursing also received clinical instruction and training in tuberculosis and other chest diseases. Large industrial firms were starting to have regular X-ray check-up of their employees, and government employees, school teachers and students as well.

On this organization, which gave promise of becoming nation-wide in scope, burst the Pacific war like a thunder-bolt from the blue.

#### PREDISPOSING FACTORS

The following factors contribute to the prevalence of the disease in the Islands:

(a) *Poor housing*: Housing was a prewar problem in itself. More than 300,000 homes were destroyed as a result of the fighting and bombings during the Pacific war, making the problem much more acute. Whole families have to double up, not in houses, but in makeshift sheds, shacks and lean-tos (the *barong-barong*) without sanitary facilities. In the razed areas of Manila and its suburbs, it is not uncommon to find three or four families squeezed into a shed measuring four by five yards, which leaks like a sieve during the rainy season and which is as hot as an oven during the summer months. Thus, spread of infection by close and continued contact is easy. The War Damage Commission could do a lot by hastening the settlement of claims, although an individual claimant cannot get more than \$500.00.

It must be mentioned here that whole communities have been wiped out in some areas, the majority of their inhabitants massacred or maimed. In Manila virtually every federal building has been demolished, century-old historic buildings gutted, and churches, museums and libraries burnt down. There is no question but there is a dearth of public buildings and private dwellings in the entire young republic to-day.

(b) *Malnutrition*: Even before the war it was an admitted fact that the Filipino race was so undernourished that every year beriberi killed more infants than did respiratory diseases. During the forty months of Japanese occupation, not only did no imports reach the Philippines due to the blockade *but the countryside likewise was stripped to feed and maintain upwards of one million unwelcome guests* (the Japanese Imperial Army had no quartermaster supplies to speak of). The Japanese saw to it that their troops lived off the fat and meat of the land, not caring whether the civilians starved. Hence, avitaminosis reared its head, and malnutrition contributed to the death of thousands.

Even now when nutrition is better, the high cost of living (the purchasing value of the peso is only one-fifth of its prewar level) is still taking its toll. Statisticians are agreed that for the next few years the cost of living will remain higher than prewar standards.

(c) *Parasitism*: Intestinal parasitism infests about 70 per cent of the population. Ascariasis, schistosomiasis, hookworm disease, tineasis and amebiasis are the most important diseases from parasites that infest Filipinos. The ascarids, hookworm, schistosomes and strongylids, as they pass through the lungs in their life cycle, may cause some injury to the pulmonary tissue in their sojourn to respective habitat in the human body. Whether in this manner they predispose

the lungs to subsequent lodgment of the *Mycobacterium tuberculosis* has not yet been fully ascertained.

It is a fact though that wide-spread parasitism in the Islands contributes not only to the production of secondary anemia but so lowers the resistance of the human host that either latent tuberculous foci or other intercurrent diseases readily break out.

(d) *Dust and fly problem*: These two problems are peculiar to the tropics—as the mosquito problem is. Tropical dust is the most abundant in the world. Philippine highways were mostly concrete or asphalted before the war, but the Japanese never did any maintenance, and thousands of heavy U. S. Army vehicles have pulverized the best of the asphalted roads during the past two years. The dust of the highways, carried away by tropical winds, gets into your eyes, your nostrils and into your every pore. Hence, respiratory diseases are frequent during the dry months, and may activate many a quiescent tuberculous focus.

As for flies, they can be found in droves every day of the year. With garbage and sewage disposal extremely inadequate after the war, food, milk and water contamination plays a considerable rôle in the spread of infectious diseases.

(e) *Difficult living conditions*: Apart from housing, the traditional low wages prevailing in the Orient and the high prices of food and all other commodities contribute to weaken constitutional resistance as a result of malnutrition. Filipinos are never milk drinkers, for, in a large majority, fresh milk produces either diarrhea or tympanism.

Wages are low and the common laborer earns an average of \$1.50 a day. Physicians in the health service in charge of a county receive not more than \$75 a month; clerks and teachers about \$65 a month.

Is it any wonder, then, that the children are so undernourished that they are an easy prey to tuberculosis and other contagious diseases?

It must be stated here in passing that World War II's aftermath will be felt in the Islands for the next decade. While vital statistics for the whole Philippines are incomplete, the tuberculosis prevalence in the city of Manila, according to the Philippine Health Bureau, has risen from the prewar figure of 9.07 per cent to 21.84 per cent, or an increase of 251 per cent. Last year, there were 2,144 deaths due to tuberculosis in Manila, or a mortality rate of 280 per 100,000 for the city. At war's end in 1945, 11,258 cases were found by the Health Bureau in the same city, out of 51,550 fluoroscopic and X-ray examinations, or a prevalence of 21.84 per cent.

#### PREWAR ACTIVITIES

The Philippine Tuberculosis Society's fourteen dispensary clinics, four provincial tuberculosis pavilions and the Quezon Institute, for a twelve-month period from 1940 to 1941, reported the following activities:

Total dispensary attendance.....	249,700
(examined by fluoroscopy, miniature or regular X-ray film)	
Home visits.....	114,620
Artificial pneumothorax insufflations.....	66,959

Other major and minor operations (at Quezon Institute).....	1,109
Laboratory examinations.....	65,455
Number of pneumothorax patients (at Quezon Institute).....	1,547
Number of admissions (at Quezon Institute).....	1,236
Number of discharges (at Quezon Institute) of which 61.5 per cent had positive sputa and 35.5 per cent had negative sputa.....	1,146

On the other hand, the Tuberculosis Control Section of the Philippine Health Bureau, during the ten-year period from 1933 to 1942, made 1,037,577 fluoroscopic and roentgenographie examinations with a prevalence rate of 6.53. The average was 103,757 examinations a year.

#### WAR DAMAGES AND CASUALTIES

The Pacific war has crippled the tuberculosis organization in the Philippines. There is no other health unit harder hit by the war than the Philippine Tuberculosis Society and its dependencies. Seven physicians on the staff died during the Japanese occupation. One was killed as a result of aerial bombing and the rest were either bayonetted to death or beheaded by the Japanese. Over 100 male patients and employees of the Quezon Institute were bayonetted to death in the last days of fighting during the liberation of Manila. Most of these patients were advanced cases and so weakened by disease and malnutrition that they could not walk alone.

Eleven dispensary clinics and four tuberculosis pavilions—two of the latter brand new—were damaged beyond repair; all their equipment and supplies lost or burned. The Quezon Institute proper, commandeered and occupied by the Japanese as a military hospital, was burned and greatly damaged by the Japanese before they evacuated it. What equipment and utilities remained after the conflagration was looted. Not only our research and clinical records since 1919 but ward, surgical, X-ray and laboratory equipment and supplies also perished during the fighting in the Walled City. Our medical and research libraries perished in the same fashion.

Damages sustained amount to at least two million dollars. Irreplaceable are our burnt medical books and literature, research records and X-ray and clinical records of patients dating from 1919.

The Tuberculosis Section of the Bureau of Health likewise lost all their mobile X-ray units—four in number.

#### PRESENT HANDICAPS

It has been sixteen months now since the Quezon Institute started operating again. The 80th U.S. Army Base hospital, which occupied the Quezon Institute for almost a year after liberation, made some repairs of the damaged buildings at the Quezon Institute, turned over their surplus to us in late December, 1945 on memorandum receipt. Some essential X-ray, surgical and clinical equipment is still lacking and some of us have grown rusty and turned into nervous wrecks with the war years, but most of the old crowd is back and new hands are being trained again. Present handicaps are plenty. Sanitary facilities are the



scarcest, for most of our plumbing and electric fixtures were lost. Foodstuffs, drugs and other commodities now are still scarce and expensive. Water mains remain unrepaired, hence there is water shortage in the Manila area. At the sanatorium it is very trying to have water only for three or four hours out of the twenty-four. That really poses a big problem in the face of some 1,200 sanatorium residents to take care of.

Our sincere thanks are due to the National Tuberculosis Association, which has aided the Philippine Tuberculosis Society in various ways. The NTA has given us an outright financial donation of \$5,000—when we were without any funds—Christmas seals, medical books, magazines, journals, educational posters, pamphlets and moving picture films, all of which not only have been of great practical and material help but also have bolstered our morale considerably. We desire to express our appreciation to many American doctors who have sent us relief supplies and medical literature.

At present we have been enabled to reopen five provincial dispensary clinics although only three of them have X-ray facilities.

The biggest problem of all is the inadequacy of funds for tuberculosis work. Even the governmental Tuberculosis Control Section, which is being aided directly by the USPHS, has the same financial problem. The USPHS has given us a \$5,000 donation for surgical equipment and two small X-ray units for which we are deeply grateful.

There are now two new miniature X-ray units under the Bureau of Health entity and 250 hospital beds for tuberculosis.

The present tuberculosis organization in the Philippines has a group of trained men and the spirit to combat tuberculosis. But it has only 1,200 beds now, where 70,000 are needed; not more than ten X-ray units, when at least twenty times that number are required. A program of expansion is on its way, depending upon available funds. The spirit is there—the spirit that made possible Bataan and Corregidor—even after the echoes of the most horrible war have just barely receded in the distance. Yet there is still “war” in this era of peace—the war against tuberculosis—as an already prostrate people succumbs at the rate of four deaths every hour, in the tuberculosis sector alone.

Notwithstanding which, the people of the Philippines go on serene and unperturbed, suffering in silence. The new Republic marches on with the Captain of the Men of Death stalking just behind. He carries a dark mantle in both hands, but life in the Philippines now—after the terrible misery and agony and devastation and cruelty of the war years—is comparatively sweet even if it is but a “tiny gleam of time between two eternities.”

# TUBERCULOSIS IN AUSTRALIA

EMIL BOGEN<sup>1</sup>

## MORTALITY

Australia has had the lowest tuberculosis death rates of any country in the world, since data first became available (8). The apparently lower figures reported in New Zealand would be greatly increased by the inclusion of their Maoris, who form 6 per cent of her population but contribute more than a third of her tuberculosis deaths (12). Since aborigines in Australia constitute less than one per cent of the total population, it is unlikely that the indeterminable tuberculosis deaths among them would greatly affect the mortality rate from the disease in the entire continent. Inquiry into the causes for the low tuberculosis death rate in Australia appears desirable, then, as it might point the way for other countries to achieve similar desirable results. (See tables 1, 2 and 3.)

Tuberculosis is not a new or unknown disease in Australia. Consumption killed the first white man to be buried there, and a number of the convicts and other early settlers are known to have succumbed to the disease, but the fragmentary information available indicates that even in its early years tuberculosis was much less common in the colonies than in the mother country (3). The disease is said to have been on the increase before the discovery of the tubercle bacillus, but its death rate, even then, was less than half of that reported in most other countries (9).

From an annual death rate of more than 160 per 100,000 in 1882, tuberculosis has declined continually in Australia up to the beginning of this war, reaching a minimum of 33 per 100,000 in 1940, when that of the United States was 45. The decline stopped, and the rates even increased during the war, or in some states before the war began, but it is difficult at this time to evaluate the real significance of this contemporary trend. The tuberculosis death rates in the different states vary, that of Queensland being generally about one-third lower than that of Victoria, but most of the differences may be accounted for by differences in the age distribution of the populations; the general low level and steady decline are found in all (13). In every country tuberculosis causes much fewer deaths among children than in the old, and this disparity is especially marked in Australia, where the quarter of the population under 15 years of age contributed only 4 per cent of the tuberculosis deaths in 1940. Correction for this factor, by applying the age and sex specific tuberculosis death rates to the standard million population used by statisticians, still leaves the Australian situation better than that of other countries (7).

## MORBIDITY

The prevalence of tuberculous infection in Australia, as revealed by tuberculin tests, has not been studied as extensively as that in the United States, but sample

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test surveys in Queensland (6), New South Wales (1), Victoria (14) and South Australia (5) demonstrate that the percentage of positive reactions encountered at the ages tested is far below that usually reported in American and European countries. Analysis of extensive series of autopsies in South Australia (4) and in Queensland reveals a much lower frequency of tuberculous lesions, active or healed, than has been reported from other countries. This is particularly marked in the lower age groups. However small and unrepresentative some of the

TABLE 1

*Tuberculosis mortality rates in Australia*

1881-1885.....	164	1901-1905.....	113	1921-1925.....	62
1886-1890.....	161	1906-1910.....	92	1926-1930.....	56
1891-1895.....	140	1911-1915.....	77	1931-1935.....	45
1896-1900.....	122	1916-1920.....	71	1935-1940.....	38

TABLE 2

*Pulmonary tuberculosis in twelve countries in two periods; and beds per annual deaths*

	1881-1885	1940	BEDS PER TUBERCULOSIS DEATHS, 1934
Australia.....	122	33	0.9
New Zealand, white.....	94	34	1.9
Denmark.....	249	37	1.8
United States.....	249	43	1.3
England and Wales.....	194	53	1.0
Germany.....	348	62	0.7
Scotland.....	210	62	1.4
Italy.....	137	59	0.6
Switzerland.....	203	73	1.7
Japan.....	101	105	0.1
France.....	255	109	0.8
Finland.....	255	179	0.3

TABLE 3

*Tuberculosis deaths and death rates in New Zealand, 1948, by race*

Deaths, white	572	Maori	354	Total	926	Cases reported	6,772
Rate	37.2	Maori	369.1	Total	60.0	Beds in institutions	1,800

samples studied may have been, and however opinions may differ as to the cause of the lowered incidence found, their unanimity indicates that tuberculous infection in Australia is less wide-spread than in other countries.

Morbidity rates estimated from annual notifications of disease, from the central registries maintained in some places, or from special surveys tend to confirm the low incidence of tuberculosis indicated by mortality rates, autopsy examinations and tuberculin tests. The apparently high fatality ratio of 0.56 deaths per new case reported annually in 1940 suggests inadequate diagnosis or reporting. Some

doctors, even tuberculosis specialists, openly stated that they did not report cases, since it only led to undesirable publicity of the disease with loss of jobs, homes, etc. by the patient but never to anything being done for him by the health authorities, while others suggested that even the deaths from tuberculosis are understated because of social prejudice against the disease or fear of consequences by the physician certifying death in a patient who had not previously been reported to be tuberculous. In a few places central registries were incomplete, or contained duplicate and obsolete entries, and the importance of prompt notification and an up-to-date tuberculosis registry was insufficiently appreciated. (See table 4.)

#### CASE-FINDING

Case-finding activities suffer from the concealment of patients and contacts because of social opprobrium attached to tuberculosis, lack of coöperation of private physicians in looking for tuberculosis or notifying cases when found,

TABLE 4  
*Tuberculosis death rates, deaths, notifications of cases and institutional beds in Australian States*

	QUEENSLAND	N.S.W.	SOUTH A.	WEST A.	TASMANIA	VICTORIA
Rate, 1940.....	28	35	37	42	43	43
Deaths, 1940.....	270	959	220	199	103	812
Notifications.....	248	1,907	276	263	248	911
Beds (1945).....	300	1,210	734	300	160	1,400

inadequate nursing force to make the necessary home visits and bring contacts in for examination, insufficient facilities for X-ray and other examinations, and refusal of contacts to report for examination and hesitancy in appealing for legal compulsion in such cases.

Fluorography with 35 mm. films, often with improvised equipment, is widely used in Australia. Candidates for the armed forces, workers at the Burnie paper mills, the Sydney transport workers, government employees in Victoria, and other large groups have been so examined, and private facilities have been made available for taking such films at low cost in various places, but there is still room for expansion of such efforts. The larger, 4 x 5 inch fluorograms are less popular than in the United States; stereoscopic films are infrequently encountered; and paper films and body section roentgenography are known only to a few men.

Sputum examination is intensively pursued by a number of men, who are using concentration and culture methods, fluorescence microscopy, and animal inoculation with typing of strains of tubercle bacilli obtained, but direct smears are more often used, and even these are too often neglected.

X-ray films of all admissions to general hospitals, to find early cases and to protect the other patients and the hospital staff from infection by patients with advanced disease, unknowingly admitted, are not yet utilized in Australia, though

repeated studies have emphasized the danger of the infection, especially to student nurses. The measures now in use in some places, tuberculin testing of nurses, refusal to accept nonreactors on tuberculosis wards, enforced vacation for those developing tuberculous infection even without other evidence of disease, need to be supplemented by case-finding efforts on all hospital admissions, and the use of adequate precautions in the care of all patients who are not known to be nontuberculous, as well as in the known consumptives.

State and voluntary outpatient clinics throughout Australia are unfortunately burdened with the care of tuberculous patients for whom there are no available hospital facilities; they are, therefore, unable to concentrate upon the case-finding and after-care programs which should be their chief concern. The ambulatory care of active cases of tuberculosis involves additional strain upon the patient who should be at rest, as well as the risk of spreading the infection among those with whom he comes in contact en route to the clinic or office consultation.

Preemployment and repeated fluorograms are taken in some industries with a silicosis hazard, such as mining, and other precautions are taken against silico-tuberculosis in their employees. Similar surveys have been attempted among factory workers, food handlers, and inmates of special hospitals, insane asylums, penal institutions, etc., where tuberculosis is unduly prevalent or dangerous, but much more remains to be done in this direction. Tuberculosis has been alleged to be frequent and fatal among the aborigines, who have little medical care, but individual cases observed indicate that they resist it much like white men, and no adequate statistical data are available (2). Tuberculosis in cattle and tubercle bacilli in market milk have been emphasized in Queensland, especially, and Australia is behind the United States both in the tuberculin testing of cattle and in the pasteurization of milk.

#### INSTITUTIONS

The most important single factor in the control of tuberculosis is the isolation and treatment of all active cases of the disease (10). Institutions for the care of the tuberculous were constructed in Australia at an early date, and increased especially during the first quarter of the twentieth century. Sanatorium construction lagged, and the number of beds actually used for the institutional care of the tuberculous even diminished in some places during the depression and second world war, but new facilities are being opened or contemplated in many places. Most Australian states have more than the old minimal requirement of one bed per annual death, but none yet even approaches the modern standard of three beds per death, and some fail to recognize the need for more adequate facilities.

Qualitatively as well as quantitatively, the tuberculosis institutions in Australia leave much to be desired. A few use the most modern forms of surgical treatment, pneumothorax, pneumonolysis or phrenemphraxis, extrapleural pneumothorax, cavity suction drainage and thoracoplasty procedures, including bilateral collapse, and even lobectomy or pneumonectomy (11). But this is the exception, available to only a small fraction of the patients whom it might save. Many sanatoria afford only custodial care to the patients who do succeed in gain-

ing admission. Rest may be prescribed in some places but rarely is such a regimen rigorously followed. Injections of tuberculin, gold preparations, cadmium, mutton bird oil, and other treatments are used by enthusiasts in some places, but medical care often consists only of periodic visits by volunteer or honorary physicians, and even this is lacking in some places.

#### PREVENTION OF INFECTION

The exceptionally low tuberculosis death rates in Australia in early years may have been due, in part, to the long journey and hard life which deterred some who knew they were affected from attempting the trip, and hastened the death of others who might else have continued to infect their neighbors. There resulted a beneficial cycle, the low incidence of open cases of clinical tuberculosis making for a lowered incidence of the infection, and the lessened spread of the infection leading to a lowered incidence of clinical breakdown.

The spread of the infection may also have been retarded by the sparseness of the population, the diminished opportunities for effective contact between individuals living in small scattered buildings, the absence of slums and their congestion, the habits of open air living and the traditional English avoidance of the physical intimacies of more effusive peoples.

More important has been the extent to which patients with advanced tuberculous disease have been placed in general hospitals, almshouses and sanatoria, or otherwise taken from their family and other contacts at a time when they are expectorating great numbers of bacilli. This was done in Australia, as in England, more than in most other countries though it is still far from satisfactorily extensive. Part of the credit for the decline in the tuberculosis mortality rate in Australia may be given to even this inadequate degree of hospitalization and isolation of the vectors of the infection.

#### RESISTANCE TO DISEASE

The low tuberculosis mortality rates in Australia may not be ascribed to genetic factors, since the English people, who belong to the same racial stock, have so much higher rates. Development of a resistant strain by the survival of those who were not susceptible to tuberculosis cannot have occurred here where tuberculosis never killed the high proportions of the population it did elsewhere, though the failure of a resistant strain to have developed through the generations which have been decimated by the disease in Central Europe should have dissipated that notion long ago.

Nutritional factors raising resistance to tuberculosis may include the high total caloric intake, or the relatively high protein content of the average Australian diet. Qualitative dietary defects, especially lack of vitamins, of minerals such as calcium or fluoride, or of roughage, and excess of simple sugar and sweets, have been alleged as the cause of excessive dental caries in Australia. Leaders of Australian dentistry and medicine, as well as foreigners and laymen, have remarked upon the poor teeth observed there, though lack of proper dental hygiene and insufficient or unskilful dentistry are also blamed.

Despite the reputed hazard of the tropics for tuberculosis, and the high rates

reported in some tropical countries, the warm dry climate of Australia has also been given credit for its health. The bright sunshine was said to kill expectorated germs, and thus lessen air-borne infection, as well as to activate protective substances and lure people into the outdoor life.

More important, perhaps, though less tangible, is the generally slower tempo of the average Australian life. The short work-day and work-week, intermissions for tea in midmorning and midafternoon, as well as for regular meals, the frequent holidays and work stoppages for other causes, may evidence the strength of the labor movement, the tradition of industrial independence, the extensive system of pensions and aids, and the absence of abject poverty. The warm climate, well educated, widely traveled and leisure loving population and economic independence lead to habitual indolence, slowness of movement, taking it easy and cooperating instead of fighting nature and man, with an absence of the rush, anxiety and pressure felt in the hectic competition of the Northern cities. This type of existence, practically resembling a continued rest cure, such as might be advised for a patient with a quiescent tuberculous infection, may well be a determining factor in the low tuberculosis rates which have been found.

#### SUMMARY

Australia has consistently reported low tuberculosis death rates. The prevalence of tuberculous infection and morbidity are likewise low. Case-finding and institutional facilities are wide-spread but inadequate. Factors affecting the spread of the infection, and conditions affecting resistance to the disease are seen in the Australian way of living.

#### SUMARIO

##### *Tuberculosis en Australia*

Australia ha comunicado constantemente bajas cifras de mortalidad tuberculosa. La frecuencia de la infección y la morbilidad tuberculosas son igualmente bajas. El sistema de descubrimiento de casos y las instalaciones institucionales están difundidos, pero resultan inadecuados. Los factores que afectan la difusión de la infección y la resistencia a la misma se encuentran en las condiciones de la vida en Australia.

#### *Acknowledgments*

This rapid survey of tuberculosis in Australia is based mainly upon personal interviews in May and June, 1945 with scores of men and women interested in tuberculosis in most of the centres in the country, including physicians and surgeons, institutional, clinic, public health and private practitioners, lay employees, volunteer workers, and patients in clinics and sanatoria. Their kindly hospitality is greatly appreciated and whatever of value may reside in this study must be attributed to their aid, though errors of fact and interpretation must be blamed on the writer and on the haste with which the visits were made. Special thanks are due to the following for information which was utilized in this survey:

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# STREPTOMYCIN-RESISTANT TUBERCLE BACILLI

Effects of Resistance on Therapeutic Results in Tuberculous Guinea Pigs<sup>1</sup>

WILLIAM H. FELDMAN,<sup>2</sup> ALFRED G. KARLSON<sup>2</sup>  
AND H. CORWIN HINSHAW<sup>2</sup>

Little precise information is available regarding the possible influence of drug resistance on the therapeutic effectiveness of streptomycin in infections produced by tubercle bacilli. It has been assumed that pathogenic bacteria in general which exhibit increased resistance against a chemotherapeutic agent *in vitro* will not likely be amenable to the therapeutic influence of the same drug *in vivo*. Clinical experience attests to the validity of this assumption.

With the increasing use of streptomycin in the treatment of clinical tuberculosis the problem of drug resistance has become exceedingly important as a limiting factor. After treatment for a few weeks to several months there is observed, in a considerable percentage of patients, a change in the *in vitro* resistance of the tubercle bacilli. Tubercle bacilli obtained from patients before treatment with streptomycin is started usually have a relatively low resistance (high sensitivity) to streptomycin *in vitro*. Conversely, tubercle bacilli observed in cultures obtained from the same patient after streptomycin has been administered for several weeks may have an *in vitro* resistance to streptomycin several thousand-fold greater than that at the onset of treatment. Under these circumstances it is generally believed that, when a streptomycin-resistant population of tubercle bacilli has largely or wholly replaced those that were sensitive to streptomycin in the first phase of the treatment, further administration of the drug usually is not warranted.

In order to determine if experimental tuberculosis infections produced by tubercle bacilli having a marked *in vitro* resistance to streptomycin would respond to streptomycin therapy the following studies were done.

## METHODS

Two experiments were conducted concurrently: one with a normally sensitive culture of tubercle bacilli having an *in vitro* resistance to 0.31 microgram of streptomycin per milliliter of medium and one with a culture having an *in vitro* resistance to more than 2,000 micrograms of streptomycin per milliliter of medium. Both cultures were obtained from the same patient. The first mentioned or normally sensitive culture was isolated from a gastric lavage specimen obtained from the patient before any streptomycin was administered. The second culture was also obtained from a gastric lavage specimen

<sup>1</sup> A review of the evidence pertaining to the effectiveness of streptomycin in experimental tuberculosis induced by tubercle bacilli sensitive to streptomycin has been published previously (1). For a recent summary of the status of streptomycin in clinical tuberculosis the report by Hinshaw, Feldman and Pyle (2) may be consulted.

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after the same patient had received streptomycin for approximately four months.<sup>4</sup> Each culture was used for subcutaneous inoculation of a separate group of 28 guinea pigs. The infective dose of tubercle bacilli for each animal was 0.1 mg. moist weight.

Twenty days after inoculation, 4 guinea pigs in each group were killed to determine the extent and character of the disease. The remaining animals in each group were then divided into 14 untreated controls and 10 to be treated with streptomycin. The daily dose of streptomycin was 6 mg. given in four equal doses at six-hour intervals.<sup>5</sup> Treatment was continued until the 166th day after infection. During this period, treatment had been given for 146 days.

At the time of necropsy, tissues were obtained for subsequent histological study from the lungs, liver, spleen, tracheobronchial lymph nodes and from the area of inoculation in the subcutis. In addition, in most instances a portion of the spleen of the respective animals in the two groups that were treated and in the groups of untreated controls was cultured for tubercle bacilli. Positive cultures were later subjected to *in vitro* tests to determine resistance to streptomycin.

### RESULTS

*Relative survival times:* The survival times of the treated and untreated animals constituting the two experiments are shown in figure 1. While there are some differences between the untreated controls in the two groups there is a marked distinction between the two groups of animals that were treated. At the end of the period of observation, 8 of the 10 animals inoculated with the streptomycin-sensitive culture and treated were living; only 2 had died. This was in marked contrast to the mortality among the guinea pigs infected with the resistant culture and treated, all but 2 of which were dead at the time the experiment was terminated.

Figure 1 indicates that the group that was treated after infection with the resistant culture did, as a whole, live somewhat longer than the untreated controls, also infected with the resistant culture.

The average survival times of the animals constituting the untreated controls in the two experiments were sufficiently dissimilar to justify brief mention. The first of the untreated animals inoculated with the streptomycin-sensitive culture died forty-four days after inoculation and the last animal in this group died 114 days after being infected. The average survival time for the group was 70.5 days. The first of the untreated controls inoculated with the streptomycin-resistant culture died thirty-two days after being infected; the last animal in this group died after 164 days. The average survival time for the 14 animals was 95.5 days. This represents an average of twenty-five days greater survival time for the group inoculated with the streptomycin-resistant culture than was true of the group infected with the streptomycin-sensitive culture. The standard error of this difference of survival time is  $\pm$  eleven days. Since the difference (twenty-

<sup>4</sup> The daily dose of streptomycin was 2 g. given in four doses six hours apart. The method for determination of resistance to streptomycin *in vitro* has been described previously (3).

<sup>5</sup> The streptomycin used in these studies was kindly supplied through the courtesy of the late Dr. D. F. Robertson, Merck & Co., Inc., Rahway, New Jersey.

five days) is more than twice its standard error, it may be considered statistically significant.<sup>6</sup> This may indicate that the bacteria which are most resistant to streptomycin are less virulent than those which are sensitive to streptomycin. Obviously, definite conclusions regarding this are not warranted from the relatively meager data obtained. Additional observations will be necessary to establish definitely the influence of streptomycin resistance on the virulence of tubercle bacilli.

The evidence from this phase of the observations indicates definitely that,

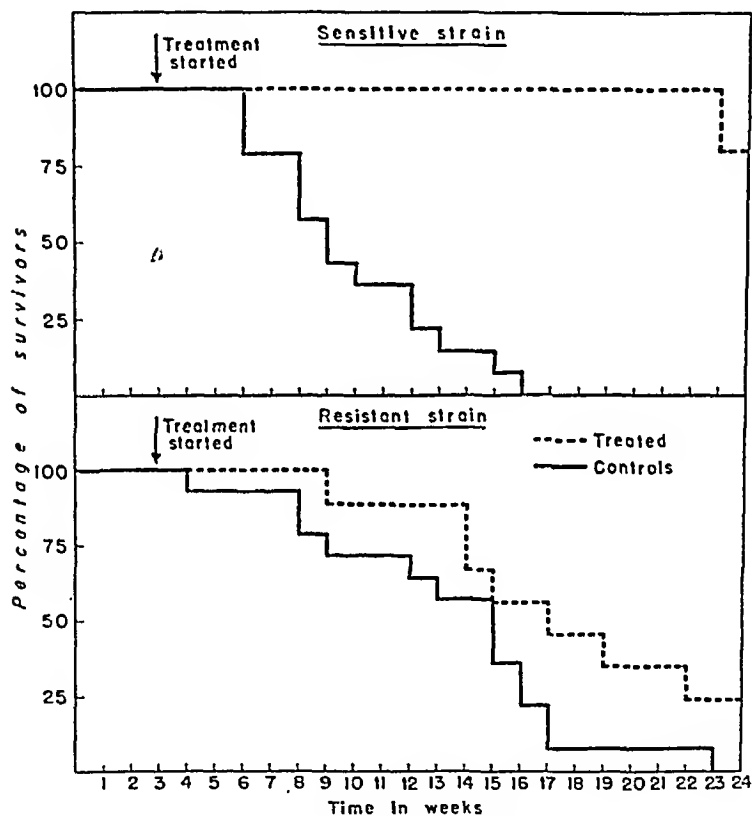


FIG. 1. Relative survival times of the four groups of animals in the two experiments.

while streptomycin may slow the tempo of the morbid processes caused by streptomycin-resistant tubercle bacilli, the ability of the drug to cope successfully with the infection caused by these bacteria is impressively diminished.<sup>7</sup>

**Pathology:** The extent and character of tuberculosis observed at necropsy in the 56 guinea pigs used in these studies are shown schematically in figures 2 and 3.

<sup>6</sup> Statistical data kindly computed by Dr. Joseph Berkson, Division of Biometry and Medical Statistics, Mayo Clinic.

<sup>7</sup> Miller (J.A.M.A., November 22, 1947, 135, 749) has reported that streptomycin may stimulate the growth of some, but not all, strains of streptomycin-resistant meningococci. We did not observe any similar phenomena with respect to the strain of streptomycin-resistant tubercle bacilli studied in our experiment.

It is of interest to note the wide-spread dissemination of the infection observed grossly in the 4 animals in each experiment that were killed twenty days after being inoculated. The infection had resulted in easily demonstrable lesions in the spleen, in the liver and, with the exception of one animal, in the lungs. From the point of view of relative virulence after twenty days, the two cultures were comparable.

As mentioned previously, the two groups of animals in each experiment that served as untreated controls had dissimilar average survival times (70.5 days and 95.5 days, respectively). However, the amount of tuberculosis recorded for the 14 animals in each group was essentially similar. The amount of disease in all of the animals was impressively severe and was presumed to have been the cause of death in each instance (figures 2 and 3).

Although the amount and severity of the disease were approximately the same in the untreated controls in each experiment, this was not true for the two groups of animals that had received treatment with streptomycin. The difference in the amount of tuberculosis in the two groups of treated animals was clearly evident at the time of necropsy (figures 2 and 3). Seven of the 10 animals inoculated with the streptomycin-sensitive culture were without gross signs of tuberculosis in the organs of predilection (spleen, liver and lungs), whereas all 10 animals inoculated with the streptomycin-resistant culture were severely affected. In fact, the degree of involvement among the treated animals in this experiment was comparable to that observed in the untreated controls (figure 4).

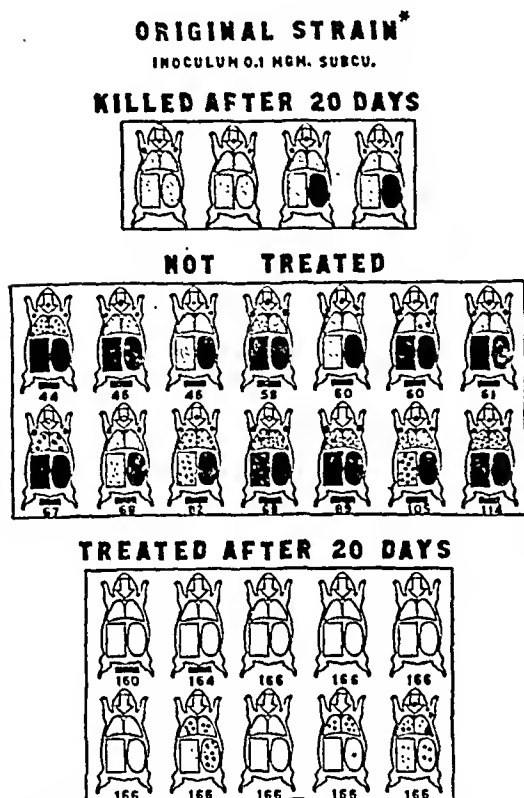
Tissues from all of the animals in both experiments were examined microscopically. This phase of the study is summarized in part in table 1. From these data the amount of tuberculosis in the two groups of untreated controls and in the group inoculated with the streptomycin-resistant culture and treated is essentially the same. This is especially impressive when these results are contrasted with the amount of tuberculosis observed in the group inoculated with the streptomycin-sensitive culture and treated. In this instance the average index of infection (based on an arbitrary maximal figure of 100) was 13.2, while the figures for the other three groups were 95, 90.5 and 91, respectively.\*

Microscopically there were no unusual histopathological features observed in the tissues from the animals inoculated with the streptomycin-resistant cultures prior to treatment with streptomycin. The disease in this group was similar in every respect to that observed in the untreated controls. The pathological process was that of an actively destructive, apparently unrestrained tuberculosis infection in which any deterrent effect of the treatment was not detected (figures 5 and 6).

The microscopic examination of tissues from the animals in the treated group that had been inoculated with the streptomycin-sensitive culture revealed an entirely different situation. In 2 of the 10 animals no lesions of tuberculosis were found in the parenchymal organs of predilection. In 5 others the disease was limited to small calcified nodules in the spleen (figure 7). As was mentioned previously, 3 of the 10 animals in this group had extensive lesions of active

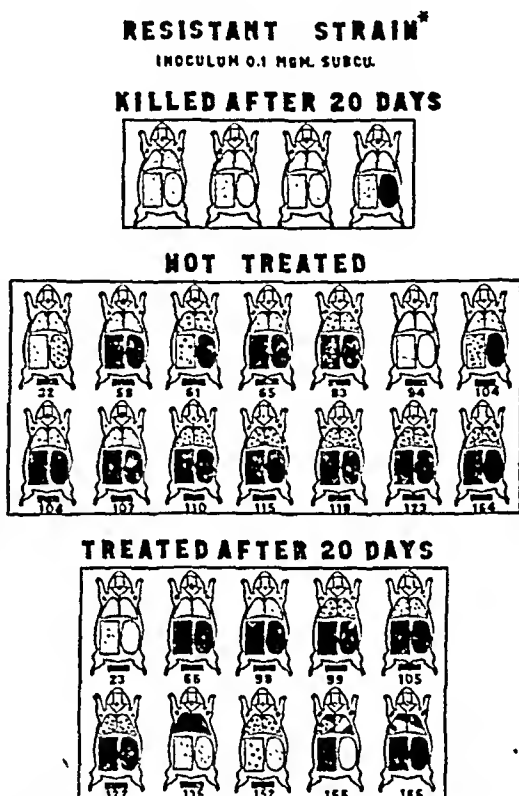
\* The scheme used to determine the index of infection has been described previously (4).

tuberculosis. In these, the lungs and spleen especially were involved. It was of interest to observe that the liver in each of the 3 animals in which the disease was



\* CULTURE USED OBTAINED FROM SAME PATIENT BEFORE AND AFTER THERAPY

FIG. 2



\* CULTURE USED OBTAINED FROM SAME PATIENT BEFORE AND AFTER THERAPY

FIG. 3

FIG. 2. Schematic representation of the 28 guinea pigs inoculated with tubercle bacilli isolated from a patient before streptomycin therapy was started. A black bar indicates that the animal died; the numeral represents the number of days the animal had been infected. Note the extent of the disease before treatment was started (top row). The difference in the amount of tuberculosis between the untreated animals and those that received streptomycin is striking.

FIG. 3. Schematic representation of the 28 guinea pigs inoculated with tubercle bacilli isolated from the patient after months of treatment. (The culture was resistant *in vitro* to more than 2,000 micrograms of streptomycin per milliliter of medium.) A black bar indicates that the animal died; the numeral represents the number of days the animal had been infected. Note that the amounts of tuberculosis in the untreated and the treated groups are comparable, indicating little if any effect of treatment.

active in the spleen and lungs was practically free of lesions. Another interesting observation pertaining to the disease in the 3 animals mentioned was the relative "age" of the lesions as judged by their microscopic appearance. Compared with



a



b

Fig. 4. *a*) Lungs, liver and spleen of an untreated guinea pig inoculated 104 days before death with a streptomycin-resistant culture of tubercle bacilli. Severe tuberculous involvement of the liver and spleen. Minimal involvement of the lungs. *b*) Lungs, liver and spleen of a guinea pig inoculated ninety-nine days before death with a streptomycin-resistant culture of tubercle bacilli and treated with streptomycin the last seventy-nine days of life. The disease is severe in each of the three organs.

the appearance of the lesions in the untreated control animals in which the infection was of comparable duration, the active lesions in the animals that re-

TABLE 1

*Average severity of tuberculosis in different organs expressed numerically\**

CULTURE	GROUP	ANIMALS	SPLEEN (MAX. 35)	LUNGS (MAX. 30)	LIVER (MAX. 25)	SITE OF IN- OCULATION (MAX. 10)	AVERAGE INDEX OF INFECTION (MAX. 100)
Sensitive to streptomycin	Controls	14	35	25	25	10	95
	Treated	10	3	7	0.27	3	13.27
Resistant to streptomycin	Controls	14	32.8	25.7	22	10	90.5
	Treated	9†	31	29	21	10	91

\* Data based on the histopathological characteristics of the tissues indicated.

† Of the 10 animals in this group originally, one died prematurely.

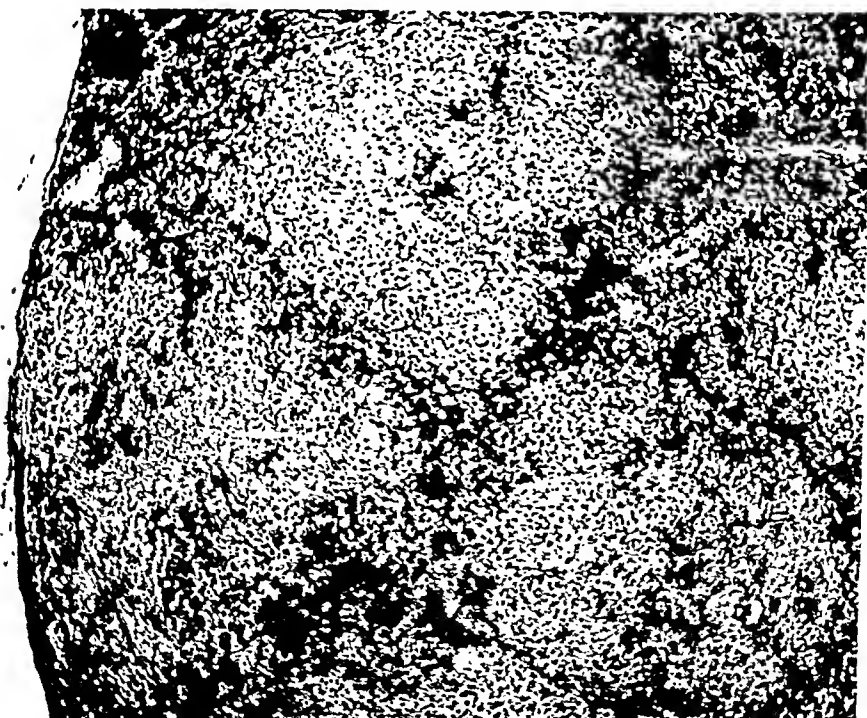


FIG. 5. Spleen of treated guinea pig infected with streptomycin-resistant culture of tubercle bacilli. Animal died sixty-six days after inoculation and had been treated for forty-six days. Numerous active tuberculous foci. ( $\times 70$ )

ceived treatment appeared to be of more recent origin. Furthermore, in some situations actively progressive lesions appeared in areas adjacent to lesions that

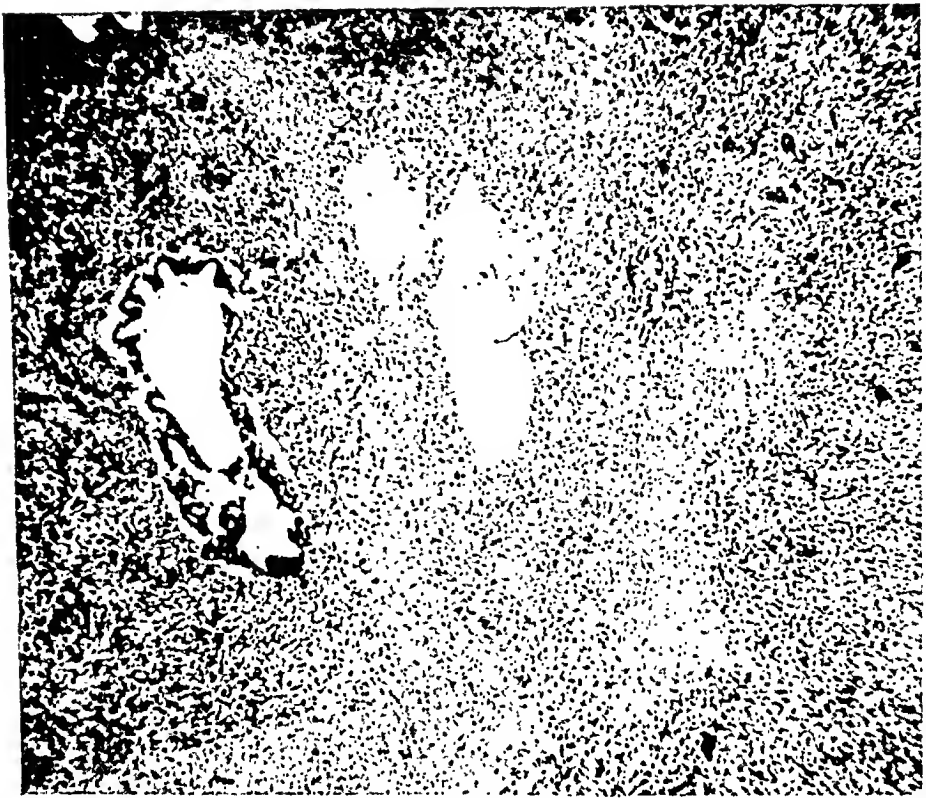


FIG. 6. Lung of treated guinea pig infected with streptomycin-resistant culture of tubercle bacilli. Animal died 122 days after inoculation and had been treated for 102 days. Destructive tuberculous lesion with early cavity formation. ( $\times 70$ )

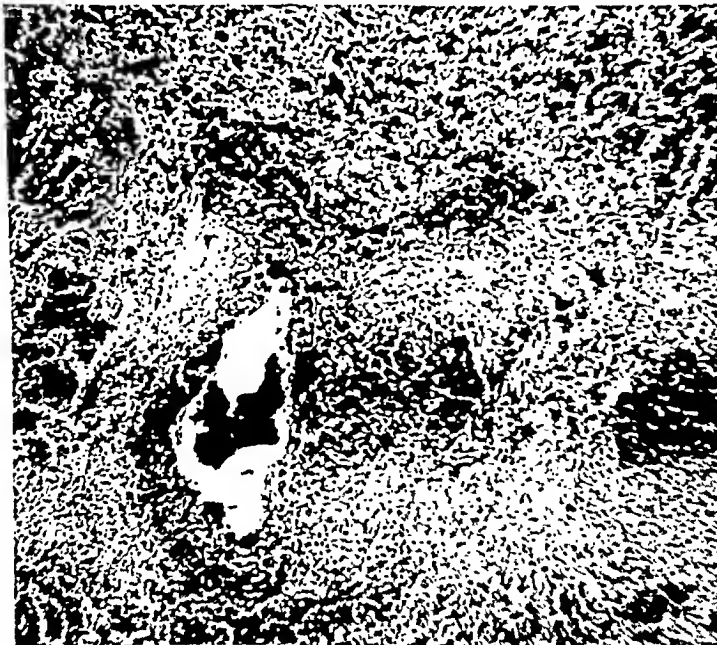


FIG. 7. Spleen of treated guinea pig, killed 166 days after inoculation with streptomycin-sensitive culture and after 146 days of treatment. The only residual evidence of tuberculous infection was a small calcified nodule. ( $\times 70$ )



were calcified and apparently inactive (figure S). A possible explanation for this unique combination of morbid changes is to be had from the results of the study of the cultures obtained from the affected tissues. These will be referred to later in this report.

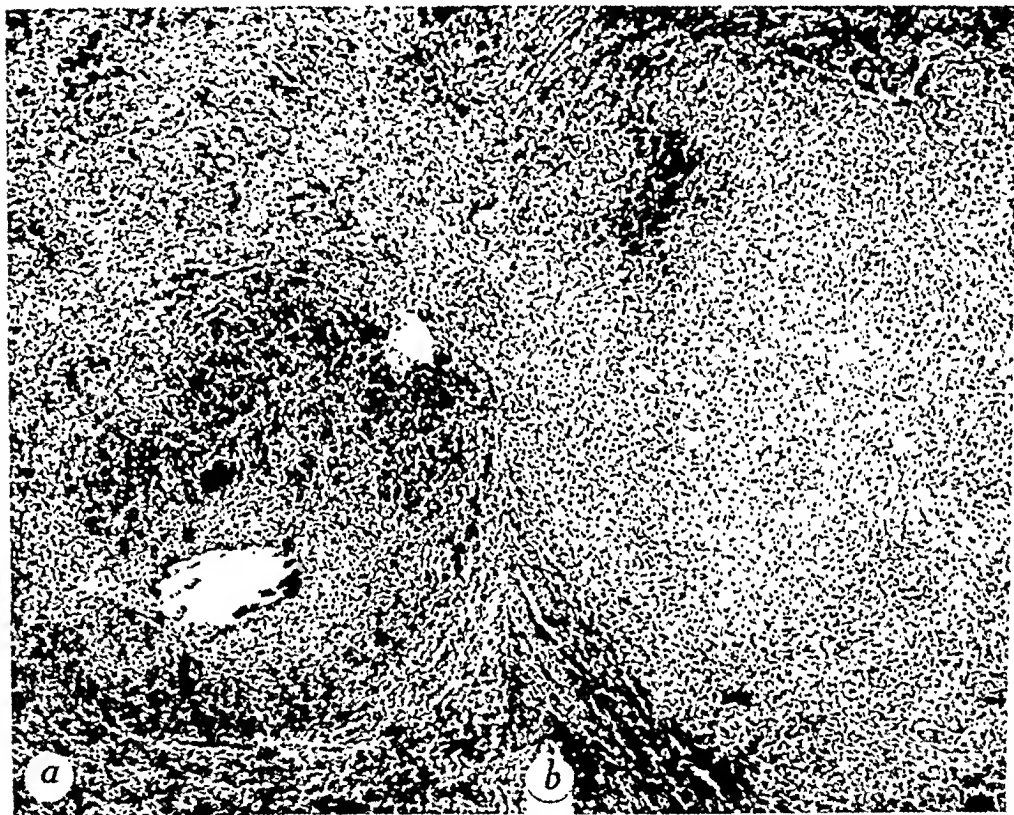


FIG. S. Spleen of guinea pig, inoculated with streptomycin-sensitive culture, which was killed 166 days after inoculation and 146 days after beginning of treatment. Tubercle bacilli having a resistance to streptomycin greater than 3,000 micrograms per milliliter were isolated from a portion of this spleen. *a*) Small calcified lesions, apparently inactive. ( $\times 70$ ) *b*) Region of active tuberculosis adjacent to calcified nodule shown in *a*. The active process appears to be of more recent origin than the lesions which are calcified. ( $\times 70$ )

*Residual infection:* Cultures of acid-fast bacilli, presumably tubercle bacilli, were isolated from the tissue suspensions prepared from each of the spleens of the treated animals inoculated with the streptomycin-resistant culture. From the spleens of the treated guinea pigs inoculated with the streptomycin-sensitive culture, attempts to isolate acid-fast bacilli failed in 2 instances and were successful in 8.<sup>9</sup>

<sup>9</sup> These results are consistent with previous experience (5) and emphasize again the suppressive rather than the sterilizing effect of streptomycin on tubercle bacilli *in vivo*.

*Streptomycin resistance of cultures isolated:* The splenic cultures obtained in both experiments from the animals that had been treated with streptomycin were subjected to tests *in vitro* to determine if residence in the animals had altered appreciably the resistance to streptomycin determined originally for the two cultures constituting the infective inocula.

The results of this portion of the study indicate that (1) the cultures obtained from the specimens of both groups of the guinea pigs, treated and controls, inoculated with the streptomycin-resistant culture had in all instances the same relative degree of resistance as the original culture; (2) of the 8 cultures obtained from the spleens of the animals inoculated with the streptomycin-sensitive culture (and treated with streptomycin), 5 had a resistance to streptomycin respectively as follows: 0.31, 0.31, 0.15, 0.08 and 0.15 microgram per milliliter of medium. Thus there was no evidence that in these 5 animals resistance to streptomycin had been altered as a consequence of treatment. Cultures were obtained from 10 of the untreated controls inoculated with the sensitive culture and all had the same rate of sensitivity to streptomycin as the original culture.

It will be recalled that 3 of the treated animals in the group inoculated with the sensitive culture had considerable tuberculosis at the time of necropsy. Microscopically most of the lesions appeared to be of recent origin and in some instances active lesions of recent origin appeared in areas where nonactive or arrested lesions also occurred (figure 8). The streptomycin resistance of cultures obtained from these 3 animals was strikingly different from that of the other cultures obtained from animals in the same group mentioned previously. Whereas the cultures obtained from the animals in which the disease had been rather successfully suppressed had a very low resistance to streptomycin, the cultures isolated from the 3 animals in which the disease was not under control had a very high resistance to the drug. The resistances of the 3 cultures were more than 2,000, more than 3,000 and more than 2,000 micrograms, respectively, of streptomycin per milliliter of medium.

These observations on the occurrence of highly streptomycin-resistant tubercle bacilli in animals inoculated with tubercle bacilli of low resistance explain the failure of streptomycin therapy to exert a continuing successful restraining influence on the infection. We are not aware of any previous reports which describe the development of resistant strains of tubercle bacilli in guinea pigs as a result of treatment.

It would appear that, during the earlier phase of treatment when the vast majority of the infective organisms were highly sensitive to the suppressive effects of the drug, the lesions that existed when treatment was started were eventually resolved or fibrosed and calcified. This was evident from the finding of lesions of different "morphological age" in the same organ.

#### COMMENT

These experiments have provided definite evidence that in the guinea pig streptomycin is not therapeutically effective if the tuberculous disease is induced

by a highly resistant strain of tubercle bacilli.<sup>10</sup> The possible clinical implications of this observation are suggested. However, one must recognize that in clinical tuberculosis the great majority of strains of *Mycobacterium tuberculosis* have relatively low resistance to streptomycin at the time when treatment is started. The expected therapeutic benefits of the drug will in some types of cases be accomplished before the streptomycin-resistant tubercle bacilli predominate. This may occur after treatment for several weeks or even several months.

During the period of treatment when tubercle bacilli of low resistance constitute most of the bacterial population, the suppression of the organisms—and perhaps the killing of some—enables the natural defenses of the patient to become, in most cases, effectively operative. As a consequence there is set in motion the complex mechanisms of resistance and repair which were latent or suppressed as long as the large majority of the infective bacteria were undisturbed in their natural progression. Once activated as a result of the action of streptomycin on the sensitive bacteria, the forces of repair seem, in most instances, to continue effectively operative. After streptomycin therapy is discontinued, even though highly streptomycin-resistant tubercle bacilli can, for a time at least, be isolated, the forces of resistance and repair are often expressed in the continued betterment of the clinical course of the disease.

The case of pulmonary tuberculosis from which the two cultures used in our two experiments were obtained is illustrative of this course of events. Streptomycin therapy of this patient was discontinued on January 1, 1946, at which time the tubercle bacilli obtained from gastric lavage specimens were highly resistant to streptomycin *in vitro* and *in vivo*. Specimens of gastric lavage were used to inoculate guinea pigs in March, April, May, June, July, August, September and November, 1946, and in no instances were signs of tuberculosis observed when the animals were killed for necropsy eight weeks after being inoculated. Consistent with these observations was the clinical status of the patient. She continued to improve and apparently the disease finally became stabilized. At the present time, sixteen months after treatment with streptomycin was discontinued, there has been no detectable reactivation of the disease.<sup>11</sup>

#### SUMMARY AND CONCLUSIONS

A study was done to determine if infections produced by tubercle bacilli having a marked *in vitro* resistance to streptomycin would respond to streptomycin therapy. Tubercle bacilli with a normal sensitivity to streptomycin were ob-

<sup>10</sup> Essentially similar results have been reported by Youmans (6) in experimental tuberculosis of mice induced by streptomycin-resistant strains of tubercle bacilli.

<sup>11</sup> Since this paper was written another gastric lavage specimen was obtained (April 9, 1947) and used to inoculate guinea pigs. Eight weeks later, when the animals were killed for necropsy, no signs of tuberculous infection were observed. A more recent report (December 20, 1947) indicates that the suppression of the disease in the patient has continued, approximately two years after streptomycin therapy was discontinued.

tained from a patient before treatment with streptomycin was started. A culture, resistant to streptomycin *in vitro*, was obtained from the same patient after treatment for four months with streptomycin. Two experiments were done concurrently. In one, guinea pigs were infected with the sensitive culture and in the other experiment a similar group of guinea pigs were infected with the resistant culture. Twenty days after inoculation, treatment of 10 animals in each experiment with streptomycin was begun. Treatment was continued daily until all of the untreated controls had died (approximately twenty-three weeks).

The results showed that the disease in the animals infected with the streptomycin-sensitive culture responded favorably to treatment. However, in 3 of the 10 animals, active lesions of recent origin were present. Streptomycin-resistant tubercle bacilli were obtained from each of these 3 animals. The disease in the animals infected with the streptomycin-resistant culture failed to yield to treatment. In this instance the amount and character of the tuberculosis in the untreated controls and in the treated group were comparable.

It is concluded that infections in guinea pigs induced by tubercle bacilli resistant *in vitro* to streptomycin are refractory to treatment with this antibiotic.

#### SUMARIO Y CONCLUSIONES

##### *Bacilos Tuberculosos Estreptomicinorresistentes*

En este estudio tratóse de determinar si las infecciones producidas por bacilos tuberculosos dotados de notable resistencia a la estreptomicina *in vitro*, responden a la estreptomicinoterapia. Antes de iniciar el tratamiento con estreptomicina, obtuviéronse de un enfermo bacilos tuberculosos que mostraban resistencia normal a la estreptomicina. Obtúvose, del mismo enfermo, después de ser tratado por cuatro meses con estreptomicina, un cultivo resistente *in vitro* a la droga. Efectuáronse dos experimentos concurrentemente. En uno se infectó a cobayos con el cultivo sensible y en el otro a un grupo semejante con el cultivo resistente. A los 20 días de la inoculación comenzó el tratamiento con estreptomicina de 10 animales en cada grupo, continuándose a diario hasta la muerte de todos los testigos no tratados (unas 23 semanas).

El resultado demostró que la enfermedad en los animales infectados con el cultivo sensible a la estreptomicina, respondió favorablemente al tratamiento, aunque en 3 de los 10 animales había presentes lesiones activas de origen reciente. De estos tres animales obtuviéronse bacilos tuberculosos estreptomicinorresistentes. En los animales infectados con el cultivo estreptomicinorresistente la enfermedad no cedió al tratamiento. La proporción y naturaleza de la tuberculosis en los testigos y en el grupo tratado eran comparables.

Dedúcese que las infecciones evocadas en los cobayos por bacilos tuberculosos resistentes *in vitro* a la estreptomicina son refractarias al tratamiento con este antibiótico.

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## BOOKS

ELI H. RUBIN: *Diseases of the Chest. With Emphasis on X-ray Diagnosis.* Pp. 685, with 355 illustrations (24 plates in color), W. B. Saunders Company, Philadelphia and London, 1947, cloth, \$12.00.

By CHESLEY BUSH

Popularity of the study of diseases of the chest has been increasing for the past few years. Rapid strides have been made by thoracic surgery giving more light to the anatomy and physiology of the chest, in addition to technical operative procedures. The advent of a new volume in this field bears witness to this.

Doctor Rubin's book is by far the best exhibition of good format and good printing that has come to our attention lately. The illustrations, many of which are in color, are exceptionally clear and well done. They alone make the book of permanent reference value.

The author states that he desires to approach this subject mainly from the viewpoint of roentgenology and he has accomplished his purpose very skilfully. In addition he has also presented his subject in a clear, practical and concise form "without neglecting basic aspects." The two-column construction of the page has given more space for his subject than would be possible otherwise. The page is a delight to the eye as a specimen of the printer's art.

The structure of the book should be praised. It is logical, complete and clear. Each subject is introduced completely with histogenesis and pathology, and certain illustrative case studies are included. We are glad to see the heart becoming recognized as a part of the chest. Doctor Rubin has included it in its relations to other chest conditions, and should be given much credit for doing so.

The subject of tuberculosis is well considered and it is to be noted that all modern methods of treatment are included, the fundamentals as well as the technical procedures. This is the first time that pneumoperitoncum as a therapeutic procedure for pulmonary tuberculosis has been included in a text-book. It is also to be noted that histoplasmosis is fully discussed in the light of recent work, providing an explanation for the tuberculin-negative person with intrathoracic calcifications.

Certainly many specialists dealing with diseases of the chest may not agree with all the statements made. There are probably few fields of medicine where wider divergences in policies and procedures exist than in the treatment of pulmonary tuberculosis. This is noticeable in various parts of the country—and in various clinics. Doctor Rubin treats the fundamentals well—but some might criticize the use of pneumothorax in tuberculous pneumonias, and others would say that the complications of artificial pneumothorax are not sufficiently emphasized. Many of us believe that, as a general rule, more than one stage of pneumonolysis should be avoided, but that continuation of a pneumothorax in which adhesions are not cut is poor treatment.

Doctor Rubin should be congratulated for the space and emphasis he has placed

on post-surgical care. The section on emergencies of the chest is also a commendable thought. The bibliographical references are carefully and critically selected; the index appears to be well prepared.

The conclusion of this reviewer is that we have here a very valuable addition to the field of medical texts, and that this volume should be a part of the medical library of those interested.

ARCHIBALD REYNOLDS JUDD: *Diseases of the Chest. Diagnosis and Treatment.* Pp. xii + 608, with 140 illustrations, Philadelphia, F. A. Davis Company—Publishers, 1947, cloth, \$9.00.

By CHESLEY BUSH

The author states that he desires to produce "a brief manual for the general practitioner." On first inspection the book appears of considerable size and weight for a brief manual, but the paper is very heavy and the type is very large—so brevity is indeed attained, possibly more than desirable for the general practitioner. There is also an effort at simplification so that he who runs may read.

The structure of the book is not beyond criticism. There is no logical sequence and subjects are discussed under headings where one does not expect to find them. Factors of resistance to tuberculosis, classification of pulmonary tuberculosis and other matters are included under the heading *Pneumothorax*. In fact, the two hundred and more pages devoted to pulmonary tuberculosis are largely occupied by expositions of technical procedures and one page is devoted to the fundamental problem of rest. The use of certain procedures and their techniques change very rapidly in our present world of progress—and consequently this book will not last as an authoritative guide. In fact, we have here an evidence that it is difficult to keep texts up-to-date even on publication. Pneumoperitoneum is not mentioned as a therapeutic procedure in the treatment of pulmonary tuberculosis, and yet it is being more widely used day by day in this country. Histoplasmosis is not found in the index although it is important in the diagnosis of pulmonary disease, as well as an entity in itself.

Tracheobronchial tuberculosis is considered as a separate disease and not as a part of pulmonary disease. And yet if any fact has impressed itself on those dealing with pulmonary tuberculosis these days, it is that the bronchial factor is present in most pulmonary lesions, and that bronchopulmonary tuberculosis is probably a better descriptive term than plain pulmonary tuberculosis. Also pleurisy with effusion is treated under diseases of the pleura—but its intimate connection with tuberculosis and pulmonary disease is hardly emphasized.

The book appears to be slanted all the way toward a surgical viewpoint. This would be satisfactory if the medical aspects were also included. Pneumonolysis occupies twenty-eight pages versus one page on rest, as an example.

In conclusion, the reviewer doubts that this book meets the requirements of the general practitioner.

LEWIS J. MOORMAN: *The American Sanatorium Association. A Brief Historical Sketch. Historical Series Number 3, pp. 72, National Tuberculosis Association, New York, 1947, paper.*

By SIDNEY J. SHIPMAN

This booklet is a valuable reference manual for those interested in the origin and background of the American Sanatorium Association, the predecessor of the American Trudeau Society. For those acquainted with the early years of the American Sanatorium Association, the historical notes will bring back a host of memories and the names of many friends who have gone before. A list of programs and committee activities which follows might be rather dull reading were it not for the fact that these activities portray vividly the changing trends of thought in the minds of those workers most interested in the management of tuberculosis during the years covered by the booklet. For example, the early controversy regarding heliotherapy in tuberculosis was a subject of many papers prior to the crystallization of thought. The early controversies regarding activity are described, a subject that bids fair to be again in the foreground of discussion because new methods have shown that it is still—or again—a moot topic. The steps that led to the formation of the American Trudeau Society are described.

Doctor Moorman's lucid and concise style contributes much to the interest in this historical development which will become increasingly valuable for reference as time goes on.

*Industry, Tuberculosis, Silicosis and Compensation. A Symposium. Prepared by the Committee on Tuberculosis in Industry of the National Tuberculosis Association and American Trudeau Society. Leroy U. Gardner, Editor. Published by National Tuberculosis Association, New York, 1945. Contributors: Paul Bamberger, Leopold Brahdy, Leroy U. Gardner, David Gould, L. E. Hamlin, Herman E. Hilleboe, B. E. Kuechle, A. J. Lanza, Ada Chree Reid, O. A. Sander, W. P. Shepard, C. D. Selby, George Wright. Pp. 126, cloth.*

By HARRIET L. HARDY

Having just attended the Saranac Symposium of 1947, the first since the war, this reviewer of *Industry, Tuberculosis, Silicosis and Compensation*, a National Tuberculosis Association monograph, understands what the late Doctor Gardner and the Association had in mind in its preparation. The dissemination of accurate knowledge of pulmonary disease in industry to those who need such material is not easy because of widely divergent training and point of view, as represented by family physician, plant physician, compensation lawyer, plant manager and safety engineer, to enumerate a few specialists concerned. This group of papers for the most part succeeds in giving the necessary data to members of different disciplines in utilizable form.



Being a physician, this reader was most interested in the chapters on the diagnosis of the pneumoconioses prepared by Dr. Hamlin, Dr. Sander and Dr. Gardner. The family physician is so often puzzled by X-ray reports including reference to a pneumoconiosis in the differential diagnosis, that he would do well to own this monograph for reference. The practitioner will be helped, in general, by the chapters on the treatment of silicosis. What is said is thoroughly safe and sound. Because of the current interest, one would like to know a bit more about present practice, though experimental, with aluminum as prophylaxis and therapy in humans.<sup>1</sup> Public health authorities and plant physicians will be gratified by the support of their efforts in promoting chest X-ray surveys provided in Part I.

Since so much was said about the engineering control of dust hazards, it might have helped the medical men and the owners of small plants, who do not have full-time engineering help, to have had a not too technical chapter on this subject.

Doubtless because the subject itself is so complex, this reviewer found Part III on compensation the least satisfactory section of the book. It is excellent to raise questions and point out responsibilities, but since the intent of the volume seemed to be primarily informative, the compensation section might have been handled differently. Doctor Brahdry has too much confidence in medical skills alone. It very often happens that a physician cannot make a correct diagnosis of occupational etiology in a given case of disease without help from a properly qualified chemist or an industrial hygiene engineer or both. The real problem here is that many physicians are not aware of this lack and do not know where to look for correct data.

Mr. Kuechle remarks, "Many times even the employer dealing with new chemicals or new combinations of chemicals is unaware of potential hazards to the health of his workers." Is it not reasonable to suggest that the employer is responsible for making certain, before he uses potentially hazardous materials, that he has all available data on the action and prevention of toxic effects, if they exist, of such material?

*Industry, Tuberculosis, Silicosis and Compensation* should be widely distributed and used to increase the usefulness of the present important chest X-ray surveying being done in industry throughout the country.

MANUEL TAPIA: *Formas Anatomoclínicas, Diagnóstico y Tratamiento de la Tuberculosis Pulmonar. Tomo II. Pp. 538, with 439 illustrations, Livraria Luso-Espanhola, Lda., Rua Nova do Almada, Lisboa—Barcelona, 1946, paper.*

By WILHELM SWIENTY

In the opening chapters of this second volume of his standard work, Doctor Tapia continues the detailed description of all those types of reinfection tuber-

<sup>1</sup> This topic is discussed in a paper by Dr. John W. Berry, soon to be published in the REVIEW, accompanied by an Editorial on the same topic by Dr. Anthony J. Lanza. [Editor]

culosis which have not been dealt with in the first volume: fibro-caseous and caseous tuberculosis, the cavity complex, atelectasis and pleural tuberculosis.

It is Doctor Tapia's contention that the definition of a cavity should be revised. Every tuberculosis starts with caseation. The defensive body reactions decide whether the further development of the disease is in the direction of an exudative-progressive or a fibrous-retrogressive process. The tissue destruction in tuberculosis is essentially cavitory. From an anatomical point of view, practically every case of tuberculosis shows destructive foci of various sizes which often cannot be visualized in the conventional X-ray film nor even in tomograms. A great number of cases with small cavities have no clinical symptoms and remain undetected during life. For this reason, the old concept which identified cavities with a far advanced process should be abandoned.

In Doctor Tapia's classification, pleural tuberculosis is regarded as a special manifestation of tuberculosis; he believes that primary pleural tuberculosis is much more common than most authors think. For the development of pleurisy, the existence of a primary focus and a particular allergic condition are necessary. If these two factors are not present, a local inflammation of the serous membranes may result with later formation of adhesions. This is in contradiction to the generally accepted opinion that the exudate is the primary step for the formation of adhesions which appear in the region of a peripheral parenchymal lesion with involvement of the pleura. Doctor Tapia's assertion that pleural obliteration and adhesions may form without pleural exudate is hard to follow.

The second half of the book is devoted to the clinical and radiological diagnosis of tuberculosis and the differential diagnosis with other pulmonary diseases. The diagnostic X-ray techniques and methods are described in detail, as are the bacteriological procedures. A critical evaluation of the sero-diagnostic tests is given. Although no one method has been satisfactory as yet, further investigation and development of the flocculation and the complement fixation tests should be encouraged, because such a specific test for tuberculosis would make early diagnosis possible in more cases than with the standard examinations of to-day.

The observations about tuberculin reactions in nontuberculous diseases are of great interest. In acute infections with or without involvement of the respiratory tract, previously positive tuberculin reactions disappeared during the acute phase of the disease in almost all of the many cases observed by the author. They reappeared slowly and progressively during convalescence. Only in miliary tuberculosis and in the terminal stages of other forms of tuberculosis does allergy wane. In Doctor Tapia's opinion, this transitory disappearance of tuberculin allergy in infections of undetermined etiology is proof of their non-tuberculous nature.

The importance of Arneth's index and of the sedimentation rate is discussed. The increase of plasma proteins is a sign of the response of the defense mechanism to the infection. New investigations may, by using the protein-globulin ratio, establish a reliable index for the prognosis of pulmonary tuberculosis.

Unusually clear X-ray positives illustrate the many case histories. Unfor-

tunately, few tomograms are used; and bronchography has been neglected throughout the entire volume, even in the chapters on bronchiectases and bronchial carcinoma. The frequent misspelling of names, the many typographical errors, the lack of a bibliographical index and the author's frequent use of his own very personal terminology ("granulitis" for miliary tuberculosis etc.) are annoying. As in the first volume, the modern Anglo-American literature is only occasionally referred to. With these exceptions, the book is recommended reading for the specialist.

MANUEL TAPIA, LUIS QUINTELA AND ANSELMO FERRAZ DE CARVALHO: *El neumotorax extrapleural*. Pp. 246, with 117 illustrations, *Livraria Luso-Espanhola, Lda., Rua Nova do Almada, 86 a 90, Lisboa—Barcelona, 1947, board.*

By A. A. MOLL

Extrapleural pneumothorax has been one of the most controversial procedures in the surgical treatment of tuberculosis. This monograph explains its foundations, its technique and its indications as well as its complications, deficiencies and disadvantages. The need of early diagnosis and the different results secured by various surgeons are pointed out. Tuffier is given credit for his pioneer work in pulmonary surgery, beginning with his pleuroparietal *decollement*—the forerunner of extrapleural pneumothorax—in 1891 and, after a series of changes including plombage, going back, in 1926, to extrapleural pneumothorax. Typical well illustrated case histories are reported to demonstrate the points emphasized. The literature cited is ample and representative, including a number of American papers, most of them published in the REVIEW, and a few from Latin America. The series of cases treated by the authors, with a follow-up period of at least six months, numbers 73; with good results in 67.2 per cent, doubtful in 8.2 per cent, and failures in 24.6 per cent. This compares to a grand total of 60 per cent of successes with extrapleural pneumothorax in the literature. The rate of successes went up to 73 per cent in 52 uncomplicated cases and 92.5 per cent in 27 "ideal" cases, but it decreased to 52 per cent in 25 patients in whom indications were liberalized. Results were somewhat better with oleothorax (78.3 per cent in 23 cases) than with pneumothorax (68.9 per cent in 29 cases). Negative findings with tomography and guinea pig inoculation are considered the measures of success. Corrected operative fatality did not exceed 2.7 per cent in the series. The so-called medical extrapleural pneumothorax sponsored by Rotta is not encouraged. Its use, however, by Medici and Sampietro in Argentina for sectioning otherwise noncuttable pleural adhesions is praised. This book is a conscientious and fair appraisal of a method in dispute by experts familiar with practically every phase of the subject.

R. O. DRABKINA: *Allergy in Tuberculosis. State Institute for Scientific Research in Tuberculosis at Kiev, 1940*

By MAX B. LURIE

This is a comprehensive review of the world literature on allergy and immunity in tuberculosis down to 1938. It also includes an original investigation on the nature and rôle of heteroallergy in tuberculosis. It presents additional evidence for the view that tuberculosis enhances the physiological activity of the reticulo-endothelial system not only against the tubercle bacillus, but also against a variety of unrelated bacteria, such as colon bacilli, streptococci and staphylococci. This is evidenced not only by an increment in the phagocytic activity of these cells for these microorganisms, as demonstrated by other workers, but also by the greater capacity of tuberculous animals to remove these microorganisms from the circulation. This increased reactivity of the reticulo-endothelial system also explains the enhanced resistance of tuberculous animals against cholera, anthrax etc. In the same category is included the observation of the greater capacity of tuberculous animals to produce nonspecific antibodies. The increased toxicity of colon bacilli for tuberculous animals is ascribed to the same mechanism; for, the activated mesenchyme of the allergic animal may release more endotoxin from colon bacilli in a given time than that of a normal animal. However, this increased sensitivity of the tuberculous animals to nonspecific irritants may have a deleterious influence on the tuberculous process. If tubercle bacilli circulate in the blood, as they do from time to time, nonspecific inflammatory processes may reactivate dormant lesions or may even induce the formation of new lesions in the joints, skin and other organs, due to the well known phenomenon of the increased permeability of blood vessels at the site of inflammation. On the other hand, tuberculous animals are at times less sensitive to toxic agents than normal animals. For example, tuberculous animals may tolerate amounts of histamine fatal to normal animals. Hence, anaphylactic phenomena are less pronounced in tuberculous animals. The author stresses the rôle of nonspecific factors such as vascular, nervous, nutritional states etc. on the intensity of the tuberculin skin reaction in tuberculous animals and the inaccuracy of the estimate of the absence of allergic sensitivity on the basis of a negative skin reaction. For this reason she does not accept as decisive the experiments on desensitization as indicating that allergy plays no rôle in immunity, for she maintains that there are no data on the sensitivity of the parenchymal cells in these skin-desensitized animals. In line with Bogomolets' observations on reticulo-cytotoxic sera, Drabkina noted that small doses of tuberculin stimulate the growth of allergic cells, whereas larger doses inhibit or kill them.

Judging from the French and German summaries, this Russian book appears to be an interesting and serious investigation of a problem of wide general importance.

ERICH URBACH AND PHILIP M. GOTTLIEB: *Allergy. Second Edition. Pp. xix + 968, with 412 figures and 64 tables, Grune & Stratton, New York, 1946, fabrikoid, \$12.00.*

By ALBERT H. ROWE

This volume discusses the theoretical, clinical and therapeutic aspects of allergy in a readable, approved and informative manner. Thoughtful study by any physician, including specialists, will increase his knowledge of the subject and his appreciation of the importance of allergic reactivities in patients. The authors and publishers are to be congratulated in presenting this work to our profession.

In the first of the three sections of the book, the fundamental knowledge, based largely on the experimental and clinical researches of the last fifty years, is extensively presented. The relation between allergy, anaphylaxis, atopy and immunity is ably discussed. Various views on allergy and immunity, especially in tuberculosis, are of interest. Theories of the origin of allergy and its effect on the body tissues are considered. Experimental anaphylaxis and allergy are described. The effect of antigens and various recognized antibodies in producing sensitization and the allergic reactions in tissues receive consideration. In this section, also, the methods of testing, the preparations of allergens and the specific and symptomatic measures available for the control of clinical allergy will be found.

In Section 2, most of the recognized and some hypothetical causes of clinical allergy are discussed. Here one finds the most recently recognized allergies, to penicillin, diodrast, gold salts and the important Rh factor. The many causes of contact allergy and the often debatable physical allergies are described. The rôle of bacterial and virus allergy in infectious diseases, producing the clinical manifestations of allergies, receives attention.

The many symptoms arising from allergic reactions in practically all tissues of the body are to be found in Section 3. Thus nasal, sinusal, bronchial, gastrointestinal, cutaneous, central nervous system, ocular, aural, cardio-vascular, hematopoietic, joint and genito-urinary manifestations of allergy, as reported in the literature, are disclosed to the reader. Because of the frequency of pollen allergy, the pollens especially necessary to consider in each of nine logical botanical divisions of our country are listed. These lists might have contained a larger number of pollens of secondary importance. References to published surveys in these various areas also would have been helpful, since many allergists believe in treatment with a large number of pollens which the patient inhales, even though skin reactions may be small or absent. The use of very weak dilutions, especially for coseasonal treatment, as advised by Hansel and Rowe, could have been noted in this section.

The discussion of all of these problems is based on many of the important contributions in the literature of the last half century. No attempt to review all of this literature has been made, accounting for the omission of many references which may seem important to various students. Many allergists, more-

over, will disagree with the writers' continued recommendation of propetans for the control of food allergy. Certain procedures which have generally been found inefficacious, such as the oral desensitization to foods, are advised without critical comment. Detailed menus and recipes for the accurate use of elimination diets could have occupied some of the space devoted to directions for the exclusion of single foods, such as egg, milk or wheat. Rarely do we see a patient allergic to only one food.

Future editions might prove of added value if statistics on large numbers of successfully treated patients with various manifestations of allergy were included, from which justified deductions concerning the usual allergenic causes and the best methods of control could be drawn. More case reports with brief specific discussions of the treatment and prolonged follow-up observations would also be valuable.

### *Books Received*

- JOHN FRANCIS: Bovine Tuberculosis. Including a Contrast with Human Tuberculosis. Pp. 220, with 36 illustrations and 21 tables, Staples Press Limited, Cavendish Place, London, W1, 1947, fabrikoid, 25'-net.
- E. GRÄUB: Tuberkulöse Reinfektion beim Rinde und ihr Einfluss auf die Resistenz. Pp. 93, 1947, S. Karger, Basel—New York, paper, Swiss francs 12.
- GERTRUDE E. HODGMAN: A Public Health Survey of Saratoga County, New York, 1945-1946. Pp. 136 + xv, survey made for the Saratoga County Tuberculosis and Public Health Association, Inc., Saratoga Springs, N. Y., paper, \$1.25.
- ARTHUR F. KRAETZER. Procedure in Examination of the Lungs. With Especial Reference to the Diagnosis of Tuberculosis. Third Edition, revised and with a Preface by Jacob Segal. Pp. xviii + 150, with 16 figures and 14 X-ray plates, New York, Oxford University Press, 1947, cloth.
- S. G. LEMAITRE: La Radiophotographie Systématique au Service de la Lutte Anti-Tuberculeuse dans la Région du Nord. Pp. 87, Édité par la Croix-Rouge Française, 12 Square Jussieu, Lille, paper.
- O. M. MISTAL: La Tuberculose dans le Monde. Preface by Prof. G. Bickel. Pp. 496, with 73 illustrations, Librairie Payot, Lausanne, 1947, paper.
- JÓN SIGURDSSON: Studies on the Risk of Infection with Bovine Tuberculosis to the Rural Population. With Special Reference to Pulmonary Tuberculosis. Acta Tuberculosea Scandinavica, Supplementum XV. Pp. 250, Einar Munksgaard, Copenhagen, 1945, paper, Dan. Kr. 15.—.

## AMERICAN TRUDEAU SOCIETY<sup>1</sup>

### Report of the Arizona Trudeau Society

Dr. William H. Oatway, Jr., *Secretary*

The affairs of the Arizona Trudeau Society seem to be in good order at the end of the first year and a half.

The 1946 fall meeting was held in Phoenix in November. Original reports were given on *X-ray Diagnosis of Endobronchial Tuberculosis, Planigraphic Studies and Interpretation and Treatment and Pathology of Hemothorax*. Dr. Ray Rumel of Salt Lake City was the guest speaker. He gave a paper on *Resection of Pulmonary Disease*. His expenses were paid by the American Trudeau Society for which the Arizona Society is grateful.

It was decided that the Constitution should be amended to decrease the number of meetings per year from two to one, and preferably to have it in the fall.

A spring letter is being prepared for the members to maintain contact as well as to give recent therapeutic data. The Tucson officers of the Society arranged for the hospital "Depot" distribution of streptomycin during the brief period of such necessity during the past fall.

The officers remain the same for 1947, due to the two-year tenure rule. The officers are: Dr. E. J. Nagoda, President; Dr. Howell Randolph, Vice-President; Dr. Lloyd Swazey, Treasurer; and Dr. William H. Oatway, Jr., Secretary.

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### Report of the California Trudeau Society

Dr. C. G. Scarborough, *Secretary-Treasurer*

The 1947 annual meeting of the California Trudeau Society will be held in conjunction with the annual meeting of the National Tuberculosis Association in San Francisco in June.

The principal activities of the California Trudeau Society during the year ending March 31, 1947 may be briefly summarized as follows:

#### *Committee Activities*

(1) The Committee which was appointed to suggest standards to be used by Health Officers in deciding criteria of communicability in tuberculosis held several meetings and presented its report.

This report was duplicated and sent to each Health Officer in the State.

(2) The Executive Committee of the Society met in San Francisco on October 18, 1946 and discussed future policies with reference to consultative clinics,

<sup>1</sup> All of the section reports published in this section were presented at the 42nd annual meeting of the American Trudeau Society, Medical Section of the National Tuberculosis Association, San Francisco, California, June 14-15, 1947.

postgraduate courses for physicians, examination of groups of patients in local communities under a plan whereby the local physicians of these patients would have the opportunity to be present for a discussion of the films and findings on these patients.

(5) The Committee on Membership was appointed as editing committee for the new Trudeau Society Directory. This preparation of the directory has been completed and it is now ready for printing. The new directory will contain 147 names.

### *Film Readings*

Members of the Society have read an approximate 300,000 X-ray films taken in mass X-ray surveys throughout the State.

### *Speakers for Medical Societies*

An increasing number of County Medical Societies have been supplied with speakers, who have addressed County Medical Society meetings. This is a healthy sign indicating the stimulation of the interest of the local medical societies in our work which has been evidenced during the year.

### *Fluorograph*

One issue of *Fluorograph* was published during the year and mailed to the members.

### *Correspondence*

Replies have been made to various persons who have written the society seeking information upon specific matters.

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## Report of the Eastern Section of the American Trudeau Society

Dr. N. Stanley Lincoln, *Secretary-Treasurer*

The nineteenth annual meeting of the Eastern Section of the American Trudeau Society was held at the Pennsylvania Hotel in New York City on Friday, November 8, 1946. The Clinical Section on Chronic Pulmonary Diseases of the Tuberculosis Conference of Metropolitan New York jointly sponsored the program and meeting.

After the usual registration, the meeting was called to order at 9:45 a.m. by Dr. Olin Pettingill, who presided. There were present 300 members and guests.

The minutes of the 1944 meeting, held at the Hotel Pennsylvania on January 21, 1944, were read and on motion accepted and ordered filed.

The report of the Secretary was read and, on motion duly made, seconded and unanimously carried, was ordered filed. (Copy added to end of this report.)

The Chairman appointed the following committees:



*Auditing Committee*

Dr. Arthur M. Stokes of Mt. Morris, N. Y.  
 Dr. John H. Korns of White Plains, N. Y.

After auditing the accounts, Dr. Stokes moved the acceptance of the Treasurer's report which was unanimously carried and the report ordered filed.

*Nominating Committee*

Dr. F. Maurice McPhedran of Philadelphia, Pa.  
 Dr. John Hayes of Saranac Lake, N. Y.  
 Dr. Hubert Boyle of Cambridge, Mass.

This committee reported as follows:

President	Dr. David A. Cooper of Philadelphia, Pa.
Vice-President	Dr. Herbert R. Edwards of New York City
Secretary-Treasurer	Dr. N. Stanley Lincoln, Ithaca, N. Y.

There being no nominations from the floor, on motion duly made, the Secretary was ordered to cast a unanimous ballot for the slate as proposed.

The following new members were proposed and, on motion made by Dr. McPhedran, duly seconded and carried, the Secretary was ordered to cast a unanimous ballot for their election.

*Active Members*

Dr. Nathan A. Goldstein, Flushing, N. Y.  
 Dr. Horace C. Reider, Bryn Mawr, Pa.  
 Dr. Marguerite D. Shepard, Hartford, Conn.  
 Dr. Alfred Ring, Jamaica, N. Y.  
 Dr. William P. McHugh, Cambridge, Mass.  
 Dr. Otto Brantigan, Baltimore, Md.  
 Dr. Arthur Robins, New York City  
 Dr. Raymond C. Ryan, Jamaica, N. Y.  
 Dr. Harry Epstein, Jamaica, N. Y.  
 Dr. John B. O'Connor, Trudeau, N. Y.

*Associate Members*

Dr. John Cannon, Scarsdale, N. Y.      Dr. Gordon Meade, Rochester, N. Y.

The scientific and luncheon meetings were held following the business session as indicated in the program.

Doctor Childress, Chairman of the Clinical Section of the Tuberculosis Sanatorium Conference, presided at the afternoon scientific session.

On motion duly made and seconded the meeting was adjourned.

*Secretary's Report*

In 1945, the membership was polled and a very real interest in a Section Meeting was expressed. But due to food rationing, restrictions on travel and shortage

of hotel space, it became apparent to the officers that it was not feasible to attempt a Section Meeting.

At the present time, the membership data are as follows:

1. Active members.....	206, including 26 still in military service
2. Associate members.....	53, including 13 still in military service
3. Emeritus.....	2
<hr/>	
4. Total.....	261

Since the previous meeting in January, 1944, 11 members have passed from us to their Great Reward; and 20 more have resigned, transferred to other sections or have been lost. Because there has been no opportunity for the election of new members, our present roster is definitely below its normal strength. Dr. Guild, former Executive Secretary of the American Trudeau Society, advised that the total membership of that body in the states covered by our Section is 850.

It should be recalled that associate members are those who are not members of the parent organization—The American Trudeau Society. Due to the exigencies of war, the Secretary has not taken any action with respect to the termination of associate membership of those who did not join the American Trudeau Society within the prescribed period of three years. It seems that in the coming year, when things have reverted to normal, the by-laws and regulations might be tactfully applied.

With respect to dues, the membership has been notably loyal. There are only 11 whose dues are in arrears three or more years, 9 whose dues are in arrears two years and 69 who have not paid for 1945.

The Section has no record of the military service of its members, except the lone fact that some were in service. If it is desirable that the Section archives contain data of this nature, then the individual members should forward such data.

Suggestions as to how your Secretary can serve you better are always welcome.

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### Report of the Florida Trudeau Society

Dr. R. D. Thompson, *President*

At the annual meeting of the State Tuberculosis and Health Association held in Miami on May 1-2, 1947, there was organized a Florida section of the American Trudeau Society with twenty-one physicians signed up. In addition there are many others who belong to the American Trudeau Society but were not at the meeting and who will become members of the Florida Trudeau Society.

Of course, the Florida Society will act as the Medical Section of our State Tuberculosis and Health Association and will always meet at a time when the State Association has its meeting. The officers will act as a Program Committee

for the Medical Section lending every assistance possible to the State Association. The officers elected were the following:

President	R. D. Thompson, M.D., Orlando, Florida
Vice-President	Isaac C. Clippes, M.D., Miami, Florida
Secretary-Treasurer	C. M. Sharp, M.D., Jacksonville, Florida

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### Report of the Illinois Trudeau Society

Dr. L. L. Collins, *Secretary-Treasurer*

We are planning a luncheon and X-ray presentation program in connection with the Illinois Tuberculosis Association's annual meeting to be held in Peoria the 28th and 29th of April. We also have a meeting planned in the early part of October with the Sangamon Medical Society at Springfield, Illinois.

A summary of a meeting held on December 10, 1946, follows: The regular fall meeting of the Illinois Trudeau Society was held in conjunction with the Medical Society meeting at Lake County Sanatorium, Waukegan, Illinois, on December 10, 1946, and was called to order at 2:15 p.m. by the President, Dr. Loewen. There were about 27 present for the afternoon meeting.

The first paper was by Dr. L. E. Joslyn, from the Abbott Laboratories, and his subject was *Sulfones and Streptomycin in Acid-fast Infections*. Dr. Joslyn's paper was discussed by Dr. Sweany and Dr. Petter.

The second paper was by Dr. M. Joannides, Chicago, Illinois. His subject was *Experiences with Differential Pressure Chamber*. Dr. Joannides showed slides and moving pictures demonstrating the action of the iron lung on tuberculosis. Dr. Joannides then gave a report on some person treated by this method. He expressed the opinion that this method of treatment has some possibilities. His paper was discussed by Dr. Bullen and also by Dr. Loewen.

The third paper was by Dr. E. A. Piszczek, Chicago, Illinois. His subject was *State Subsidy for Care of Tuberculous Patients*. This paper brought out a rather large discussion by Dr. Tucker, Dr. Bryan, Dr. Newitt and Mr. Shahan.

The fourth paper was by Dr. V. A. Lennarson, Waukegan, Illinois. He presented a case of *Tuberculosis of the Inner Ear*. The case was a boy aged 10 years who had a paralysis of the left side of his face and a tuberculosis of the temporal bone. A recess of fifteen minutes followed the discussion of the last paper.

A business meeting was called to order by the President, Dr. Loewen, at 5:30 p.m. . . . Dr. Bosworth, chairman of the nominating committee, presented the following slate for the consideration of the members of the Trudeau Society: President, Dr. Petter; President-Elect, Dr. Bulley; Vice-President, Dr. Webb; Secretary-Treasurer, Dr. L. L. Collins. Two members for the executive committee, Dr. Loewen and Dr. Turner. Dr. Bosworth moved that the report of the

nominating committee be accepted and that a unanimous ballot be cast for the persons nominated. Dr. Bryan seconded the motion. Motion carried.

Dr. Bryan then presented a request by Dr. Herbolzheimer of the State Department of Health requesting that the Illinois Trudeau Society make recommendations for the tuberculosis control program in the State of Illinois. A committee was appointed and this committee met at Rockford at 1:00 p.m. on December 8, 1946. Those present were: Chairman, W. J. Bryan, M.D.; Robinson Bosworth, M.D.; Kenneth Bulley, M.D.; Charles Petter, M.D.; and Arthur Webb, M.D. Mr. W. P. Shahan, Executive Secretary of the Illinois Tuberculosis Association, was present by invitation and acted in an advisory capacity.

Consideration was given as to the advisability of developing tuberculosis divisions in general hospitals in lieu of sanatoria. The committee, however, felt that this was not wise; and Dr. Bosworth moved that, because the need for tuberculosis beds is great in several areas of the State of Illinois, and because tuberculosis departments or divisions of general hospitals may not be expected to solve the problem satisfactorily, and because due regard should be given to the fact that the care of tuberculous patients in the State of Illinois be financed by specially authorized sanatorium taxes, and because such monies set aside for tuberculosis should be used for the control and eradication of tuberculosis, and because the establishment of wings or divisions in general hospitals might be conducive to the use of such funds for other purposes, and because the recognized difference in the per capita cost of general hospitals and sanatoria might result in increased costs in the care of such tuberculous patients, and because such an arrangement might bring about the neglect of proper epidemiological programs, therefore, be it resolved that this committee is not in favor of the construction or setting aside of tuberculosis divisions in general hospitals for the care of tuberculous patients at this time. The motion was seconded and carried unanimously.

The committee, however, did not wish to discourage the care of tuberculous patients in general hospitals and recommends that any teaching hospital set aside not over 10 per cent of its beds for the diagnosis, study and outline of treatment of tuberculosis patients for teaching purposes among its doctors, internes, residents, students, and nurses, but that such patients should not receive permanent sanatorium care in such general hospitals. The committee, therefore, recommends that all general hospitals be encouraged to establish communicable disease wards and that tuberculosis be considered in the same light as other communicable diseases. The committee further recommends and urges that all general hospitals establish tuberculosis case-finding procedures among its staff and patients and that all patients in the out-patient department, as well as those admitted to the hospital proper, receive an X-ray film of the chest as part of their general physical examination. It is also recommended that the staff and employees have X-rays of the chest at regular intervals.

Following dinner, Dr. C. H. Harrison, Waukegan, Illinois, gave a very interesting and informative paper on *Ocular Tuberculosis*. He presented a very interesting case. Many of those present viewed the eye ground with an ophthalmoscope.

A Clinical-Pathological Conference on *Diseases of the Chest* was conducted by Dr. J. C. McCarter, Evanston, Illinois. Several very interesting chest cases were presented and discussed by those present.

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## Report of the Indiana Trudeau Society

M. A. Auerbach, *Executive Secretary*

The annual meeting of the Indiana Trudeau Society was held May 7, 1947 at the Lincoln Hotel, Indianapolis, and, following the usual short business session, the following program was given:

*Resection for Pulmonary Tuberculosis*—Francis X. Byron, M.D., Section of Thoracic Surgery, University Hospital, Ann Arbor, Michigan.

*Laboratory Methods of the State Board of Health with Particular Reference to Tuberculosis*—Samuel Damon, Ph.D., Director, Bureau of Laboratories, Indiana State Board of Health.

12:00 noon—Luncheon.

*Chemotherapy in Tuberculosis with Special Reference to Streptomycin*—Karl H. Pfuetze, M.D., Superintendent and Medical Director, Mineral Springs Sanatorium, Cannon Falls, Minnesota.

In the afternoon a joint session was held with the Indiana Tuberculosis Association as follows:

*Some Aspects of Sensitivity to Histoplasmin and Tuberculin*—Michael L. Furcolow, M.D., Kansas City, Missouri.

*Management of Tuberculosis in Heavy Industry*—E. H. Carleton, M.D., Inland Steel Corporation, East Chicago, Illinois.

*Case-work in the Psychosomatic Approach to the Tuberculous Patient*—Jeanette Hertzman, Assistant Chief, Social Service Section, Veterans Administration, St. Louis, Missouri.

*The Chest Survey in a General Hospital*—Harold C. Ochsner, M.D., Methodist Hospital, Indianapolis, Indiana.

The elected officers are:

President	—Hubert B. Pirkle, M.D., Rockville
President-Elect	—O. T. Kidder, M.D., Fort Wayne
Vice-President	—Thomas R. Owens, M.D., Muncie
Secretary-Treasurer	—C. J. McIntyre, M.D., Indianapolis
Executive Secretary	—M. A. Auerbach, Indianapolis

## Report of the Trudeau Society of Los Angeles

Dr. Arthur E. T. Rogers, *Secretary-Treasurer*

The roster of active members of the Los Angeles Trudeau Society has passed the number of one hundred during the year of 1947, with the following serving as officers for the current year:

President	Edward S. Kupka, M.D.
Vice-President	Joseph L. Robinson, M.D.
Secretary-Treasurer	Arthur E. T. Rogers, M.D.

Regular business and scientific meetings have been held every month, including symposia prepared by the staffs of the Olive View Sanatorium, the San Fernando Veterans Administration Hospital and the Los Angeles Sanatorium. A joint meeting was also held with the Section on Radiology of the Los Angeles County Medical Association.

Attendance at the various meetings varied from 50 to 70 per cent of the membership, and papers covering many aspects of chest diseases were presented, with considerable emphasis on tracheobronchial tuberculosis, streptomycin therapy in tuberculosis and its complications, and pulmonary resection in the treatment of tuberculosis and malignancy.

The Society meets on the fourth Tuesday of every month from October to May, and physicians visiting the West Coast are always welcome guests.

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## Report of the Massachusetts Trudeau Society

Dr. William R. Martin, *Secretary-Treasurer*

The Massachusetts Trudeau Society held three regular meetings during the year 1946, in January, May and October. These meetings, since the onset of the war, have been held at the Harvard Club, Boston. Beginning with the next meeting in May, 1947, we are planning to resume our custom of meeting at the various sanatoria throughout the State.

At the fall meeting in October, it was voted to increase the membership from 100 to 125 in order to admit new members. The present membership is 105.

The present officers are:

Dr. Richard Sweet	—President
Dr. Donald King	—Vice-President
Dr. William R. Martin	—Secretary-Treasurer

Officers are elected for the year at the annual meeting which is held in May.

## Report of the Michigan Trudeau Society

Dr. L. C. Manni, *Secretary-Treasurer*

The annual meeting of the Michigan Trudeau Society was held on November 7, 1946 in Detroit, Michigan.

At this meeting it was planned to have two meetings in 1947—the Spring meeting to be held with the Michigan Tuberculosis Association.

Forty-one new members were elected to membership. The following officers were elected to serve until the Spring meeting of 1947:

Charles R. Smith, M.D., President

W. L. Brosius, M.D., Vice-President

L. C. Manni, M.D., Secretary-Treasurer

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## Report of the Minnesota Trudeau Medical Society

Dr. Clarence Siegel, *Secretary-Treasurer*

The following is a report of the proceedings of the Minnesota Trudeau Medical Society, beginning June 1, 1946.

The annual summer meeting of the Minnesota Trudeau Medical Society was held at Nopeming Sanatorium, Nopeming, Minnesota, on July 8, 1946.

Dr. Fenger gave a report of the Sanatorium Consultation Committee which met at Brainard, Minnesota, on April 28, 1946. Cases were discussed from the following Sanatoria with recommendations for treatment: Otter Tail County, Lake Park, Sand Beach, Lake Julia, Fair Oakes Lodge, Deerwood Sanatorium.

This committee met again at Pembine, Wisconsin, with the Michigan and Wisconsin groups. Various cases of thoracoplasty, phrenic, and pneumothorax operations were presented and discussed by each state.

The following scientific program was presented:

*Activities of the Nopeming Sanatorium Outpatient Department*—Dr. Robert Davies, Nopeming, Minnesota.

*Pneumoperitoneum*—Dr. Sam Sandell.

*Pneumothorax*—Drs. Clive R. Johnson and Gustav A. Hedberg.

The annual meeting of the Minnesota Trudeau Medical Society was held at the Lowry Hotel, St. Paul, Minnesota, on November 8, 1946. Forty-five members and guests were present.

Dr. Fenger gave a report of the Sanatorium Advisory Committee which had met at Walker, Minnesota, on October 11 and 12, 1946. Forty-eight Indian patients were discussed and suggestions made regarding treatment.

The Nominating Committee, consisting of Doctors Mattill, Sandell and Huban, made the following report:

Dr. Corwin Hinshaw—President

Dr. E. P. K. Fenger—Vice-President

Dr. Clarence Siegel—Secretary-Treasurer

The report of the Nominating Committee was unanimously accepted. The following scientific programs were presented:

*Treatment of Hemorrhage*—Dr. R. V. Ebert.

*Differential Diagnosis of Pulmonary Masses*—Dr. Dan Fink.

A moving picture *Technique of Mass X-ray Survey*—State Department of Health.

The annual winter meeting of the Minnesota Trudeau Medical Society was held at the Nicolet Hotel, Minneapolis, Minnesota, on January 31, 1947. Fifty members and guests were present.

Dr. Fenger also reviewed the functions of the Pembine meeting. This meeting will be held in September, 1947. A motion was made and seconded that the additional seven men be chosen by the president to attend this meeting.

Dr. Sandell suggested that, in view of the money the society had, a guest speaker be asked to be on the program in the future, and that the society pay his expenses.

A motion was made by Dr. Hedberg and seconded by Dr. Mariette that the Executive Committee be authorized to choose a guest speaker to talk on BCG or otherwise, the society paying his expenses.

The following scientific program was presented:

*Early Diagnosis of Cancer of the Lung*—Dr. Leo Rigler.

*Some Difficulties in Diagnosing Cancer of the Lung*—Dr. Frances King.

The annual spring meeting of the Minnesota Trudeau Medical Society will be held at the Mayo Foundation House on Tuesday, May 20, 1947. A luncheon at the Mayo Foundation House will be held at 12:00 noon.

The following scientific program will be presented:

*Technique and Discovery of Malignant Cells in Sputum*—Dr. J. R. McDonald, Rochester, Minnesota.

*New Data on Correlation between Mitral Stenosis and Pulmonary Tuberculosis*—Dr. D. T. Carr, Rochester, Minnesota.

*Trachobronchial Tuberculosis Treated with Streptomycin*—Dr. A. M. Olson, Rochester, Minnesota.

*Upper Lobe Carcinoma Which Might Be Confused with Tuberculosis*—Dr. O. T. Clagett and associates, Rochester, Minnesota.

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### Report of the Mississippi Valley Trudeau Society

Dr. John D. Steele, *Secretary*

The 1946 meeting of the Mississippi Valley Trudeau Society was held at the Hotel Sherman, Chicago, Illinois, on September 26 and 27. The medical program was of excellent quality and was well received. Free discussion took place on practically all papers, being especially free following the papers presented by Doctor Holm and Doctor Custer.



The following program was presented:

Thursday, September 26

9:00 a.m.

*Epidural Anesthesia in Thoracic Surgery*—Y. F. Fujikawa, M.D., Arnaldo Neves, M.D., C. A. Brasher, M.D., Mt. Vernon, Missouri; and W. W. Buckingham, M.D., Kansas City, Missouri.

*A Method of Performing Bilateral Bronchographic Studies*—H. W. Schmidt, M.D., Rochester, Minnesota.

*The Diagnosis of Right Heart Enlargement by Angiocardiography (A Preliminary Report)*—Nathan Grossman, M.D., Milwaukee, Wisconsin.

*BCG Vaccination in Denmark*—Johannes Holm, M.D., Copenhagen, Denmark.

2:00 p.m.

*Current Medical Research in Tuberculosis*—Henry Stuart Willis, M.D., Detroit, Michigan.

*The Need for Coöperation in Rehabilitation of the Tuberculous*—C. K. Himmelsbach, M.D., Sr. Surgeon, U.S.P.H.S., Chicago.

*The Physician's Role in Rehabilitation of the Tuberculous*—Norvin C. Kiefer, M.D., Surgeon, U.S.P.H.S., Washington, D. C.

Discussion.

*Our Voluntary Health Agencies*—William P. Shepard, M.D., President, National Tuberculosis Association, San Francisco, California.

*Tuberculosis Control among Hospital Personnel*—H. McLeod Riggins, M.D., President, American Trudeau Society, New York, New York.

Discussion.

8:30 p.m.

X-ray Conference.

Friday, September 27

9:00 a.m.

*Evaluation of 1945 Thoracic Surgery in a County Tuberculosis Hospital*—Karl P. Klasen, M.D., George M. Curtis, M.D., and W. L. Potts, M.D., Columbus, Ohio.

*Pregnancy Occurring in a Group of Tuberculous Women*—Gertrude F. Mitchell, M.D., Detroit, Michigan.

*Analysis of Tuberculin Testing in a Large Sanatorium*—M. R. Lichtenstein, M.D., Chicago, Illinois.

*Tuberculosis Control through Coöperation*—Edward W. Custer, M.D., South Bend, Indiana.

The business session was held on September 27 with Dr. E. S. Mariette presiding. The president called for the report of the nominating committee. This committee, consisting of Drs. F. L. Jennings, A. A. Pleyte and W. J. Bryan, presented the following nominations:

President-Elect—Dr. Herbert L. Mantz

Vice-President —Dr. Paul D. Crimm

Secretary —Dr. John D. Steele

These candidates were elected by unanimous ballot.

## Report of the Missouri Trudeau Society

Dr. D. L. Coffman, *Secretary-Treasurer*

The annual meeting of the Missouri Chapter, American Trudeau Society, was held Saturday, October 19, 1946, at 7:30 p.m., Hotel Missouri, Jefferson City, Missouri; E. E. Glenn, M.D., President, presiding. The following were present: R. M. James, M.D.; W. L. Gist, M.D.; Geo. D. Kettelkamp, M.D.; W. G. Gunn, M.D.; Chas. A. Brasher, M.D.; Newell R. Ziegler, M.D.; T. E. Huber, M.D.; John Kalish, M.D.; Bernard Friedman, M.D.; H. S. Miller, M.D.; Ira Lockwood, M.D.; H. L. Mantz, M.D.; John A. Saston, M.D.

The minutes of the previous meeting were read and approved.

The Nominating Committee reported the following slate:

President-Elect —Paul Murphy, M.D., St. Louis  
Secretary-Treasurer—D. L. Coffman, M.D., Kansas City

*Executive Committee*

E. E. Glenn, M.D., Springfield  
Geo. D. Kettelkamp, M.D., St. Louis

Moved by Dr. Mantz that the report be accepted and the secretary instructed to cast the ballot. Seconded by Dr. Miller. Carried.

Report of Membership Committee by Dr. Mantz on qualifications for membership.

*Old business*—None.

*New business*—The executive secretary was instructed to enlarge the membership list and be sure to include all St. Louis Trudeau members.

Dr. Mantz, Program Committee, spoke regarding next meetng. There was general discussion of time, place and contacts.

Dr. Kettelkamp reported on the Tri-State Conference, Coronado Hotel, St. Louis, February 9 and 10, 1946.

Dr. Mantz discussed the 1947 Tri-State meeting to be held February 22-23, Hotel Edgewater Beach, Chicago, Illinois. The sanatoria to report are: Mount Vernon (Missouri State Sanatorium), Chicago Municipal Tuberculosis Sanitarium, and Sunnyside of Indianapolis. There will be 60 cases from each institution—consecutive cases starting July 1, 1944.

Dr. R. M. James, Division of Health, spoke briefly.

The meeting was turned over to Dr. Mantz, Program Chairman, for the scientific session.

The Tri-State Trudeau Society (Missouri, Indiana and Illinois) met at the Edgewater Beach Hotel, Chicago, February 22 and 23, 1947.

The Missouri State Sanatorium, Chicago Municipal Sanitarium and the Marian County of Indianapolis Sanatorium each presented 60 consecutive admissions from January 1, 1945. Response at this meeting was much better than last because it was felt those in attendance were becoming more familiar with one another.

The Missouri Trudeau Society met again March 30, 1947, at the Hotel President, Kansas City, Missouri, just prior to the meeting of the Missouri State Medical Society. An excellent program was presented and ended with an X-ray conference in which a number of interesting and unusual films were presented.

Results of the election of officers:

President-Elect	—Jesse E. Douglas, M.D.
Executive Committee Member	—H. L. Mantz, M.D.
Secretary-Treasurer	—D. L. Coffman, M.D.

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### Report of the South Carolina Trudeau Society

Dr. Samuel E. Miller, *Secretary and Treasurer*

The South Carolina Trudeau Society met at the Wade Hampton Office Building, Columbia, South Carolina, November 1, 1946.

Doctor W. Atmar Smith, Vice-President, presided.

Doctor John M. Preston acted as Secretary and Treasurer, in the place of Doctor John F. Busch.

Fourteen physicians were present.

The following officers were elected:

President	—Dr. John M. Preston, Columbia
Vice-President	—Dr. David B. Gregg, Charleston
Secretary and Treasurer	—Dr. Samuel E. Miller, State Park

Treasurer reported income of sixteen dollars without any disbursements for past year.

Dues of one dollar each were collected from each member present for current year.

Resolution was adopted for the appointment, by the President, of a committee to consult with the State Division of Tuberculosis Control on the matter of *Minimum Standards for Physicians, Technicians, Laboratories and Others*, who are to aid that department in tuberculosis work.

These appointments will be made by the President at a later date.

The scientific program consisted of an address, with lantern slides and X-ray films, by Dr. David Waterman of Knoxville, Tennessee. His subject was *An Evaluation of Extrapleural Thoracoplasty*. He discussed the history of thoracoplasty, improvement in technique, the lower mortality, selection of cases, operative technique, complications and end-results.

## Report of the Southern Trudeau Society

Dr. J. B. Naive, *Secretary-Treasurer*

The Southern Trudeau Society met in the Assembly Room of the Mayflower Hotel, Jacksonville, Florida, on October 3, 1946. The occasion was a luncheon and reorganizational affair, there being no formal program. The meeting was under the direction of the President, Dr. Duane Carr.

Officers elected were:

President —Dr. Kellie Joseph, Birmingham, Alabama  
Vice-President—Dr. M. D. Bonner, Jamestown, North Carolina  
Secretary —Dr. J. B. Naive, Knoxville, Tennessee .

In a general discussion regarding future programs, it was the consensus that such programs should, as far as possible, take the pre-war form, that X-ray clinics should be strongly stressed and that an effort should be made to develop the strongest possible one-day scientific program. The officers were instructed to act as a program committee and were further instructed to participate with the program committee of the Southern Tuberculosis Association in the development of a program for the 1947 meeting. It was unanimously voted to request the "time and place committee" of the Southern Tuberculosis Association to hold that meeting in Birmingham, Alabama. A total of 39 were present.

There will be another meeting of the Southern Trudeau Association to be held in connection with the next meeting of the Southern Tuberculosis Conference. This meeting will be held at the Rice Hotel, Houston, Texas, October 2, 3 and 4, 1947.

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## Report of the Texas Trudeau Society

Dr. T. R. Jones, *Secretary*

The Texas Trudeau Society was organized primarily as a sponsoring group for the Scientific Section of annual meetings of the Texas Tuberculosis Association. The Society assumed full responsibility for the Scientific Section of our 1946 annual meeting, and is doing the same thing this year—in fact, plans for the 1947 program are practically complete.

There follows the minutes of the 1946 meeting of the Texas Trudeau Society.

The Texas Chapter of the American Trudeau Society met in Houston at luncheon in the Rice Hotel on Monday, September 16, 1946, during the annual meeting of the Texas Tuberculosis Association. The meeting was called to order by the President, Dr. H. Frank Carman. A total of 42 physicians were present.

In opening the meeting Dr. Carman expressed the thanks of the Chapter for the excellent program prepared for the medical section of the annual meeting

under the direction of Dr. J. Edward Johnson, Chairman of the Program Committee. Those serving with Dr. Johnson were Dr. E. G. Faber, Tyler; Dr. James E. Dailey, Houston; Dr. Howard E. Smith, Austin; Dr. Robert J. Nanks, Waco.

Minutes of the previous meeting of the Chapter, held in Austin on September 18, 1944, were approved as read. Attention was called to the fact that no meeting of the Society had been held since the organization meeting on that date, due to conditions of war which precluded large gatherings because of the difficulty of travel.

Report of the Nominating Committee was presented by the Chairman, Dr. J. Edward Johnson. The following slate was nominated to serve for the fiscal period 1946-1947:

President	—Dr. E. G. Faber, Tyler
President-Elect	—Dr. Elliott Mendenhall, Dallas
Vice-President	—Dr. James E. Dailey, Houston
Secretary	—Dr. Thomas R. Jones, Houston

There being no nominations from the floor, on motion by Dr. J. B. McKnight; the report of the Nominating Committee was adopted and these officers duly elected.

Attending the luncheon as a guest was Dr. Ward L. Moald, Surgeon, U.S.P.H.S., Assistant Regional Representative, Federal Security Agency, Office of Vocational Rehabilitation, Kansas City, Missouri, who congratulated the Society on the fine scientific program prepared for the medical section. Dr. Moald spoke briefly on vocational rehabilitation and its relation to the tuberculosis patient, stressing the important rôle which the physician plays in the program. He expressed appreciation for the coöperation which is being given Mr. J. J. Brown, Director of Vocational Rehabilitation in Texas, by members of the medical profession.

Dr. Carman commended the program of rehabilitation being carried on in Texas, saying that patients can be returned to work without any difficulty through the rehabilitation service. He extended the thanks of members of the Society to Dr. Moald for his attendance at the meeting.

There being no further business, the meeting was declared adjourned. These minutes were presented by Dr. Mendenhall, former Secretary of the Society.

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### Report of the Wisconsin Trudeau Society

Dr. Helen A. Dickie, *Secretary-Treasurer*

The Wisconsin Trudeau Society met at Lake View Sanatorium on April 26, 1947.

The entire meeting was devoted to the use of streptomycin in tuberculous disease. The first part of the meeting consisted of presentations of the cases

which had been treated from four sanatoria. Dr. Nicholas D'Esopo of Sunmount, New York, reported 25 cases which had completed 120 days of streptomycin therapy. The usual dosage was 1.8 grams per day. All of the patients had tubercle bacilli in the pulmonary secretions which were sensitive to streptomycin. At the end of four months of treatment 50 per cent of these patients' sputum contained tubercle bacilli which were highly resistant to streptomycin. Eleven of the 25 patients remained sputum-positive by smear and in all of them the organisms were resistant at the end of the period of treatment. Dr. D'Esopo concluded that exudative disease responds well initially and that cavities seldom close with streptomycin therapy. There appears to be a definite correlation between sensitivity of the tubercle bacillus to streptomycin and the therapeutic response.

Presentations of somewhat smaller groups of streptomycin-treated cases were given by Dr. G. D. Guilbert from Wood, Wisconsin; Dr. J. C. Dundee from the Veterans Hospital at Waukesha, Wisconsin; and Dr. D. Gutheil of Muirdale Sanatorium. Their results were essentially the same as noted previously, that is, many cases showed early response, but that cavity closure and complete control were seldom realized except in the early predominantly exudative lesion.

Dr. Guy P. Youmans of Northwestern University presented a paper on *The Effect of Streptomycin Therapy on Tubercle Bacilli in vitro and in vivo*. He found that all the tubercle bacilli studied were sensitive to streptomycin initially, but that the degree of sensitivity varied with strains. Twenty-nine of 131 cultures required more than one microgram of streptomycin per milliliter to inhibit growth initially. If the tubercle bacilli were exposed and reexposed through culture transfers to streptomycin a marked resistance to the drug occurred in fifty-two to 120 days. Mice infected with streptomycin-resistant strains of tubercle bacilli were not protected by streptomycin. The significance and probable method of development of resistance was discussed.

Dr. Karl Pfuete of Cannon Falls, Minnesota, stressed the importance of making use of the temporary control of the disease to proceed with the usual and accepted forms of collapse therapy. For a certain number of patients, streptomycin can be of great value in controlling the toxemia and recent spreads so that major collapse methods can be done to combat the older foci, especially cavitation, which respond poorly to the drug.

A short business meeting was held. The major discussion was concerned with joining the Wisconsin Anti-Tuberculosis Association as a group. A constitution was submitted by the committee composed of Drs. Schmidt, Daniels and Feld. This was accepted by the members and will be presented to the Board of Directors of the Wisconsin Anti-Tuberculosis Association for their approval. Dr. Feld was elected as the fifth member of the executive council.

## AMERICAN TRUDEAU SOCIETY

At the meeting of the Council held in Houston, Texas on September 30, 1947, the following appointments to committees for 1947-1948 were confirmed.

### I. Administrative<sup>1</sup>

#### *Budget Committee*

Howard W. Bosworth, M.D.  
H. Corwin Hinshaw, M.D.  
David A. Cooper, M.D.  
Henry Stuart Willis, M.D.  
H. McLeod Riggins, M.D.  
Theodore L. Badger, M.D.

#### *Nominating Committee*

Sidney J. Shipman, M.D., *Chairman*  
John H. Skavlem, M.D.  
Rollin D. Thompson, M.D.

#### *Membership Committee*

Chesley Bush, M.D., *Chairman*  
Grover C. Bellinger, M.D.  
Russell S. Henry, M.D.

#### *Constitution and By-Laws Revision*

Carl R. Howson, M.D., *Chairman*  
Herbert R. Edwards, M.D.  
Ralph Horton, M.D.  
H. McLeod Riggins, M.D.  
John D. Steele, M.D.

### II. Professional Education

#### *American Review of Tuberculosis* *Official Journal—Editorial Board*

Emil Bogen, M.D.	Lewis J. Moorman, M.D.
Halbert L. Dunn, M.D.	D. W. Richards, Jr., M.D.
Ross Golden, M.D.	William P. Shepard, M.D.
A. J. Lanza, M.D.	Sidney J. Shipman, M.D.
Herbert C. Maier, M.D.	John D. Steele, M.D.
C. Eugene Woodruff, M.D.	

#### *Annual Meeting Program (Medical Session)*

Herbert C. Maier, M.D., <i>Chairman</i>	
W. Reece Berryhill, M.D.	Arthur W. Newitt, M.D.
Cedric Northrop, M.D.	Arthur M. Stokes, M.D.
Max Pinner, M.D. ( <i>ex officio</i> )	

#### *Diagnostic Standards Revision (1) (2)*

Ralph Horton, M.D., <i>Chairman</i>	
Ezra Bridge, M.D.	Oscar A. Sander, M.D.
W. Edward Chamberlain, M.D.	John D. Steele, M.D.
Herman E. Hilleboe, M.D.	Ismael Cosio Villegas, M.D.
Edgar Medlar, M.D.	George J. Wherrett, M.D.
Hector Orrego Puelma, M.D.	Roy A. Wolford, M.D.

<sup>1</sup> The members of the Executive Committee, the Council and the Advisory Board were listed on page 609 of the December, 1947 issue of the Review.

- (1) *Subcommittee on Evaluation of Laboratory Procedures*  
 C. Eugene Woodruff, M.D., *Chairman*  
 Emil Bogen, M.D.  
 Edwin A. Doane, M.D.  
 M. L. Furcolow, M.D.  
 Max Lurie, M.D.  
 Edgar Medlar, M.D.  
 Mr. William Steenken (NTA)
- (2) *Subcommittee on Tuberculin Testing*  
 Joseph D. Aronson, M.D., *Chairman*  
 Florence B. Seibert, Sc.D.  
 Carroll E. Palmer, M.D.  
 Sol Roy Rosenthal, M.D.

*Medical Education—National Committee (1) (2)*

- Kirby S. Howlett, Jr., M.D., Chairman*
- |                          |   |
|--------------------------|---|
| Theodore L. Badger, M.D. | Max Pinner, M.D.                          |
| John B. Barnwell, M.D.   | John D. Steele, M.D. ( <i>Secretary</i> ) |
| Robert G. Bloch, M.D.    | Harold G. Trimble, M.D.                   |
| Paul T. Chapman, M.D.    | James J. Waring, M.D.                     |
| Kendall Emerson, M.D.    | George J. Wherrett, M.D.                  |
| Herman E. Hilleboe, M.D. | Henry Stuart Willis, M.D.                 |
| Edward N. Packard, M.D.  | Julius L. Wilson, M.D.                    |
| Howard M. Payne, M.D.    | Mr. C. W. Kammeier (NCTS)                 |
- (1) *Subcommittee on Faculty and Curriculum*  
 John D. Steele, M.D., *Chairman*  
 Theodore L. Badger, M.D.  
 Esmond R. Long, M.D.
- (2) *Subcommittee on Courses for the General Practitioner*  
 Harold G. Trimble, M.D., *Chairman*  
 Herman E. Hilleboe, M.D.  
 J. A. Myers, M.D.  
 Edwin J. Simons, M.D.

*Committee on Medical Education*

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 Donald S. King, M.D., *Co-Chairman*  
 Hugh B. Campbell, M.D.  
 John C. Ham, M.D.  
 Kirby S. Howlett, Jr., M.D.  
 Paul S. Phelps, M.D.  
 Alton S. Pope, M.D.  
 John W. Strieder, M.D.  
 Miss Mabel Baird (NCTS)

*Region II*

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Stuart Sanger, M.D.  
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 Paul Dufault, M.D.  
 Cedric Northrop, M.D.  
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 Raymond H. Runde, M.D.  
 C. M. Sharp, M.D.  
 Russell E. Teague, M.D.  
 Peter A. Theodos, M.D.  
 John H. Urabee, M.D.

*Rehabilitation*

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 N. Stanley Lincoln, M.D.  
 William H. Roper, M.D.  
 Thomas N. Sheen, M.D.  
 Joseph B. Stocklen, M.D.  
 Mr. Holland Hudson (NTA)  
 Mrs. C. O. DeLaney (NCTS)

*Medical Advisory Committee on Health Education*

Arthur A. Pleyte, M.D., *Chairman*  
 William H. Oatway, Jr., M.D.  
 Olin S. Pettingill, M.D.

**III. Medical Research and Therapy***Committee on Medical Research and Therapy (1) (2) (3) (4)*

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 Charles A. Doan, M.D.  
 Rene J. Dubos, M.D.  
 H. Corwin Hinshaw, M.D.  
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 Karl F. Meyer, M.D.  
 H. McLeod Riggins, M.D.  
 Florence R. Sabin, M.D.  
 David T. Smith, M.D.  
 Francis J. Weber, M.D.

(1) *Laboratory Subcommittee*

C. Eugene Woodruff, M.D., *Chairman*  
 Martin Cummings, M.D.  
 William H. Feldman, M.D.  
 Max Lurie, M.D.  
 C. Richard Smith, M.D.  
 Charles R. Smith, M.D.

(2) *Therapy Subcommittee*

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 Daniel Jenkins, M.D.  
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(3) *Chemotherapy Subcommittee*

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 J. Burns Amberson, M.D.  
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 H. Corwin Hinshaw, M.D.  
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(4) *Laboratory Subcommittee on Chemotherapy*

Guy P. Youmans, M.D., *Chairman*  
 H. Corwin Hinshaw, M.D.  
 C. Eugene Woodruff, M.D.  
 Mr. William Steenken (NTA)

## IV. Exchange of Scientific Information with Foreign Countries

(Committees to be appointed)

Latin America

Europe

Asia

## V. Joint Committees

The Medical Section will be represented on committees of the U. S. Public Health Service, American Hospital Association, American Medical Association, Office of Vocational Rehabilitation, and the National Tuberculosis Association.

(The names of the committees and personnel will be announced later.)

## AMERICAN TRUDEAU SOCIETY

### Postgraduate Courses in Thoracic Diseases

The following postgraduate courses in thoracic diseases are being planned for the early part of 1948 by the American Trudeau Society, the Medical Section of the National Tuberculosis Association.

Under the auspices of nine regional committees, covering all States and Canada, the Society's program of postgraduate medical education is being carried out in coöperation with the medical schools of leading universities.

A subcommittee on continuation study of chest diseases for the general practitioner has recommended a pilot study for a national plan. The aim is to bring the general practitioner directly into contact with survey work, interpretation of X-ray films, and to assist him in the handling of cases in his area, and in his practice. Information concerning this course will be given in a subsequent issue of the REVIEW.

March 22-26, 1948 *Region V* (States of: Ohio, Indiana, Michigan, Illinois, Wisconsin, Missouri, Iowa and Minnesota)

American Trudeau Society in coöperation with the Detroit Department of Health and Wayne University College of Medicine, at Herman Kiefer Hospital, Detroit, Michigan. *Chairman:* Dr. Paul T. Chapman, Herman Kiefer Hospital. *Registration fee:* \$50.00.

March 22-27, 1948 *Region III* (States of: Maryland, Virginia, West Virginia, Kentucky, Tennessee, North Carolina, South Carolina, Georgia and Florida, and the District of Columbia)

American Trudeau Society in coöperation with the Medical Schools of the University of North Carolina and Duke University, at Chapel Hill and Durham, North Carolina. *Chairman:* Dr. H. Stuart Willis, North Carolina Sanatorium, McCain, North Carolina. *Registration fee:* \$50.00.

April 5-17, 1948 *Region I* (States of: Maine, Vermont, New Hampshire, Massachusetts, Connecticut and Rhode Island)

American Trudeau Society in coöperation with the Medical Schools of Harvard University, Tufts College and Boston University, at Boston, Massachusetts. *Chairman:* Dr. Theodore L. Badger, 264 Beacon Street, Boston, Massachusetts. *Registration fee:* \$100.00.

April 12-24, 1948 *Region IV* (States of: Alabama, Arkansas, Louisiana, Mississippi, Oklahoma and Texas)

Plans not yet completed. *Chairman:* Dr. Julius L. Wilson, Prytania and Aline Streets, New Orleans 15, Louisiana. *Registration fee:* \$100.00. Course to be held at Dallas, Texas.

## *NATIONAL TUBERCULOSIS ASSOCIATION*

### **Exhibit at Annual Meeting in New York**

Plans are being made for a scientific exhibit to be held in connection with the annual meeting of the National Tuberculosis Association at the Hotel Pennsylvania, New York, New York, June 15 to 18, 1948, according to an announcement by Dr. William H. Roper, Chairman of the Scientific Exhibit Committee.

Individuals interested in exhibiting material dealing with various aspects of tuberculosis and also nontuberculous pulmonary disease are invited to submit, not later than March 1, a preliminary description of the proposed exhibit. The description should be sent to Dr. William H. Roper, Director, Research Section, Army Medical Research and Development Board, P. O. Box 6027, Fitzsimons General Hospital, Denver 8, Colorado.

Because of space limitations, the Committee has stated it reserves the right to use its discretion in the final selection of material.



# THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

VOLUME LVII

FEBRUARY, 1948

ABST. No. 2

**Bronchial Stenosis.**—Different aspects of pathogenesis and treatment of endobronchial stenosis are analyzed in three articles and illustrated by case histories. The first communication demonstrates the importance of bronchoscopic treatment: in a case of left pneumothorax with marked stenosis of the left main bronchus and endobronchial vegetations and ulcerations, bronchoscopic aspirations and topical applications of adrenalin were performed followed by monthly dilations with catheters of increasing caliber. Considerable improvement and enlargement of the bronchial lumen were observed on bronchoscopy, also confirmed by lipiodol studies. There was an increase in transparency of the previously opaque hemithorax. Concomitantly a marked clinical improvement was noted. The sputum became negative. This type of treatment has not provoked any complications in the above case as well as in similar cases. The second article gives the description of a progressive tuberculous stenosis of the trachea and both main bronchi in a case of cavitory disease of the left upper lobe, treated by thoracoplasty. Endobronchial treatment consisted in aspirations, adrenalin and silver nitrate applications following which the ulcerations healed. The local treatment was combined with the treatment of Charpy (40 injections of Sterogyl and 60 injections of calcium gluconate intravenously). There was, however, an increasing formation of fibro-sclerotic tissue leading to progressive, ascending stenosis of marked degree. The third article gives examples of bronchial stenosis in childhood tuberculosis. A case of tuberculoma of the right main bronchus

with atelectasis of the right lower lobe and the right middle lobe is interpreted as a rare example of primary bronchial tuberculosis. In cases of epituberculosis the narrowing of the bronchial lumen was partly due to edema of the bronchial wall, partly to thick obstructing secretions. The rôle of enlarged tuberculous lymph nodes in the development of bronchostenosis and their perforation into the bronchial lumen is described.—*Intérêt des dilatactions dans les sténoses tuberculeuses des bronches souches*, P. Mounier-Kuhn & L. Meyer; *Évolution endoscopique d'une sténose trachéale progressive chez une tuberculeuse*, P. Mounier-Kuhn & L. Meyer; *Les sténoses bronchiques de la période primo-sécondaire*, A. Dufourt & P. Mounier-Kuhn, *Rev. de la tuberc.*, 1947, 2: 64-72.—(V. Leites)

**Ballooned Cavities.**—Four cases are described in which ballooning of a cavity consecutive to pneumothorax and pneumonolysis was treated with intracavitary aspiration of air through the thoracoscope. In all cases endobronchial disease with bronchial narrowing was present. One or several aspirations of 30 to 50 cc. of air were performed with immediate effect on the size of the cavity. There was concomitant atelectasis of the corresponding lobe and development of a sero-fibrinous effusion. A few days after the intervention there was again some enlargement of the cavity in all cases, which, however, did not reach the initial size. Following this, all 4 cases showed progressive diminution and finally disappearance of the cavity within three to four months. Several hypotheses are advanced to explain the mechanism of this

therapeutic procedure when a check-valve type of bronchial stenosis was obviously responsible for the ballooning of the cavity. It is claimed that bronchoscopy consecutive to the intervention showed improvement of the bronchial involvement.—*Ponctions de cavernes soufflées sous pneumothorax. Quatre cas favorables*, H. Despeignes, *Rev. de la tuberc.*, 1947, 2: 747.—(V. Leites)

**Hemorrhagic Pleurisy.**—While relatively common, the detection of a hemorrhagic pleural effusion does not usually settle the diagnosis. The experienced clinician may, however, use the coexistence of effusion and bleeding as the starting point for his deductions. No symptom is conclusive for differentiation before a puncture settles the matter. The presence of practically pure blood in the pleural cavity usually means malignancy or hemopneumothorax. Even an increased lymphocyte count does not rule out cancer. In neoplastic cases the course may be either insidious or accompanied by conspicuous symptoms, such as pain in the neck or arms, and pressure on adjacent organs without inflammatory phenomena. A small effusion with little fibrin, clotting tendency and hemolysis in the supernatant fluid also suggests cancer. Absence of sepsis is also corroborative. A number of conditions, including amebiasis, rheumatic disease, malaria, syphilis and pulmonary disease, may be present when an excess of eosinophils is present. If there is considerable respiratory difficulty, peripheral cyanosis, sensorial disturbances, high irregular fever and enlarged liver and spleen, miliary tuberculosis is a strong possibility, especially when the effusion is bilateral. Hemorrhagic pleural effusion is uncommon in chronic tuberculosis, it being more frequently an allergic manifestation in the secondary stage or associated with miliary tuberculosis. Argentine clinicians, in opposition to Norris' observations, find it but seldom in tuberculosis cases. The literature is exhaustively reviewed. One case of transitory hemorrhagic pleurisy in cancer, and 2 typical cases, one fatal, in tuberculosis, are reported

at length.—*Pleurcias hemorrágicas*, S. Zabudovich, *Prensa méd. argent.*, April 25, 1947, 34: 748.—(A. A. Moll)

**Treatment of Genital Tuberculosis.**—Treatment of epididymal tuberculosis must be approached in the light of the new allergic conceptions. The degree of progressiveness must be determined, and the tuberculin test, X-ray studies, sedimentation rate, the Velez' and Arneith's indices and Schilling's count will help. If a progressive trend is apparent, a radical operation may prove dangerous, and the best policy seems to be watchful waiting in severe cases and a two-stage operation in milder ones. Actual epididymectomy is reserved for the second step. The first step, for which the writer claims credit, consists in an anastomosis of the deferent ducts which are attached through their sheath to the overlying inguinal skin. This preliminary procedure isolates the organs threatened from the infecting genital focus and furnishes a desirable physiological rest to the tissues.—*Tratamiento de la tuberculosis genital en el hombre*, J. Lockhart, *Prensa méd. argent.*, April 25, 1947, 34: 757.—(A. A. Moll)

**Hutinel's Disease in Mexico.**—Four cases, 3 of them fatal, of enlarged liver with tuberculous pericarditis in children are described. They were all seen in the Children's Hospital in Mexico City between May, 1915 and October, 1946. Diagnosis is rather difficult as the onset is insidious and the modalities vary and sometimes the etiology is determined only by the necropsy findings. History, tuberculin tests, search for the tubercle bacillus, X-ray studies, tomography and cardio-electrography are, however, of real help. Prognosis is most serious and only in a few cases has surgery a chance, and this only in controlling the tuberculous infection. The patient still alive was to be treated with streptomycin before surgical measures were tried. Hutinel, however, described in his original report (1893) cases in which the disease had lasted several years. While tuberculosis is the most common cause, other factors may

also be responsible. For this reason and because of Pick's significant contribution, it is argued that the condition should be known as Hutinel-Pick's syndrome. In the Children's Hospital from its opening to August 31, 1946, there were 773 cases of tuberculosis among 15,678 admissions (4.93 per cent), meningitis (255 cases), pulmonary (239), bone-joint (127) and miliary types (28) heading the list.—*Tuberculosis cardiohepatica en el niño (síndrome de Hutinel-Pick)*, L. Berlanga Berumen, *Bol. méd. d. Hosp. inf., México*, March-April, 1947, 4: 184.—(A. A. Moll)

**Miliary Tuberculosis with Heart Involvement.**—In a 4-year-old boy, who had suffered from malaria when 2 years old, a diagnosis of pulmonary tuberculosis was made on entering the hospital. The condition progressed, with jaundice and finally meningitis developed and he died. The autopsy disclosed miliary involvement of both lungs, liver, spleen, bowel, meninges, and, most uncommon, heart and large blood vessels. Enlarged nodes filled the mediastinum and mesentery, two of these masses pressing upon the gall-ducts. A large node on the lower surface of the right lung was considered to be the primary focus. The tuberculous character of the lesions was confirmed by histological and bacteriological studies.—*Tuberculosis generalizada*, M. Salas, E. Contreras R. & J. Unda, *Bol. méd. d. Hosp. inf., México*, March-April, 1947, 4: 207.—(A. A. Moll)

**Tuberculous Endocarditis.**—A case of late primary pulmonary tuberculosis in a 26-year-old female, followed by generalized miliary tuberculosis, tuberculous endometritis and tuberculous endocarditis of the *chordae tendineae*, is described. There were no clinical signs of the endocarditis and the EKG was normal. The hematogenous dissemination occurred during the course of a pregnancy. The infant died of tuberculous pneumonia twenty-five days after birth.—*Über Endocarditis tuberculosa und kongenitale Lungen-tuberkulose*, M. Aufdermaur, *Schweiz. Ztschr. f. Tuberk.*, 1947, 4: 199.—(B. Gerstl)

**Tuberculoma of Myocardium.**—Myocardial tuberculosis occurs in three forms: (1) miliary, (2) nodular, (3) infiltrating. A 20-year-old colored man was seen who died with the signs and symptoms of chronic moderately advanced pulmonary tuberculosis with serofibrinous involvement of the left pleura and multiple cold abscesses. There were no symptoms or signs of a cardiovascular involvement. On autopsy, in addition to tuberculosis of lungs and other organs, there were found three tuberculous nodules in the left auricle: one was at the base of the mitral valve, 2 cm. in diameter, and two smaller ones were in the myocardium of the left atrium.—*Tuberculoma of the Myocardium: A Case Report*, S. M. Rauchwerger & R. J. Rogers, *Am. Heart J.*, August, 1947, 34: 280.—(G. C. Leiner)

**Radiography in Tuberculosis of Esophagus.**—On the basis of 2 cases verified by biopsy and autopsy, and 4 more reported in the literature, the roentgenographic changes produced by tuberculosis of the esophagus are described as those of ulceration, stenosing infiltration or tumor. Signs of ulcer and infiltration are more suggestive of tuberculosis but there is no characteristic pathognomonic X-ray change.—*Röntgenbefunde bei Oesophagus-tuberkulose*, M. Lüdin, *Schweiz. Ztschr. f. Tuberk.*, 1947, 4: 257.—(B. Gerstl)

**Treatment of Lupus with Vitamin D2.**—The authors briefly review the clinical manifestations and pathology of *lupus vulgaris*. They cite the work of Charpy who described the treatment of *lupus vulgaris* with vitamin D2. The technique is simple: vitamin D2, crystalline, in alcoholic solution, is given in dosage of 600,000 international units by mouth three times the first week, two times the week following, and once for the next three weeks. It is necessary that calcium be given in adequate amounts along with this treatment. They recommend 50 grains a day. The authors describe 2 cases of rather disfiguring *lupus vulgaris* which were considerably benefited by this treatment. They state that the treatment is simpler than other forms and



seems to be more efficacious.—*Lupus tuberculeux et vitamine D2*, E. Gaumond & J. Grandbois, *Laval m'ed.*, June, 1947, 12: 571.—(A. T. Laird)

**Tuberculous Adenopathy.**—Case report of a 46-year-old male in whom caseo-pneumonic tuberculosis with multiple cavitations in the right upper and middle lobe was associated with a right paratracheal adenopathy. There was evidence of a calcified primary complex in the right upper lobe. Bronchoscopy revealed a perforation of the caseous lymph node into the bronchial system, between the orifices of the right upper lobe and right middle lobe bronchi. The outcome was fatal. The particular interest of this observation is seen in the fact that the above findings, which are commonly encountered in primary tuberculosis, occurred here in a case of tuberculosis which was definitely of the reinfection type.—*Rupture endo-bronchique d'une ad'noopathie médiastinale de réinfection chez un sujet de 46 ans. Pneumonie nécrotique consécutive*, J. Brun, J. Viallier & Moindrot, *Rev. de la tuberc.*, 1947, 2: 762.—(V. Leites)

**Labyrinthine Function in Streptomycin Therapy.**—A series of 23 patients receiving streptomycin therapy for at least two months was studied for auditory and vestibular function. Fifteen patients were given 1.8 g. per day in divided doses every three hours, 8 received 2.0 g. daily; all subcutaneously administered. Audiometer tests were done every two weeks during the period of treatment; all but one of the 23 patients maintained a normal audiogram. The one exception was a demerol addict who showed a 65 db. loss for 3 tones: 2018, 4096 and 8192. She was an exceptional case in that she showed no caloric responses before, during or after 121 days of 1.8 g. of streptomycin per day. Almost all of the patients had vestibular signs

or fourth week of treatment, varying in onset from eleven to sixty days in 17 patients. Although subjective vertigo lasted one to two weeks in most patients, vestibular function tests showed persistent abnormalities. All but 3 of the patients developed loss of reaction to rotation and caloric stimulation when treatment was continued for more than twenty-five days. The gait of 6 ambulatory patients showed a broad base and some ataxia after three to four weeks of treatment but compensation gradually took place so that in four months incapacity was not perceptible if vision were unobstructed and the walking surface smooth. Unsteadiness was revealed in walking on graded slopes or with vision obstructed. Walking was almost impossible in the interval between the beginning of a changed response to caloric stimulation and final occurrence of a negative response. Three months after the negative response first occurred, they did quite well under ordinary conditions. It was noted that patients over 60 showed less ability to compensate in walking, although the younger patient did very well. No recovery of response to caloric stimulation has been observed up to four months after cessation of therapy in these patients. Rotation tests showed no effect on patients who received the streptomycin, in contrast to normal subjects who show nystagmus, past pointing and ataxia after rotation. Tilting the affected patients on a table showed delayed response to changes in position. Localization of the lesion is still conjectural in streptomycin treated patients. Loss of rotation and caloric response with tilt-table response being of the peripheral type suggest a labyrinthine lesion. So far, there is no convincing pathological evidence that this assumption is correct.—*Tests for Labyrinthine Function following Streptomycin Therapy*, A. Glorig & E. P. Fowler, *Ann. Otol. Rhin. & Larynx*, June, 1947, 56: 579.—(P. Q.)

was blurred vision while reading, appearing about the same time that a fine nystagmus with lateral gaze in either direction could be detected. Vertigo usually began in the third

**Antibiotic Chlorocycline.**—Studies were made on the antibiotic properties of substances present in the mycelia and conophores of

the mushroom *Clitocyba candida*. The mushroom grows in the French and Swiss Alps. It forms characteristic, indented circles, called "witches' circles," with patches of dead plants, killed by the mushroom. The fact that these plants remained well preserved for a long period indicated the presence of an antibiotic agent (the author prefers the term "abiotic"). For experiments *in vitro*, the following method was employed: Appropriate nutritive media were inoculated with the microorganism to be tested, and poured into Petri dishes. Pieces of the mycelium or morsels of blotting paper soaked with varying concentrations of the extract were placed upon the surface of the Petri dishes and incubated. Clear areas formed around the morsels which were devoid of microorganisms. One of the extracted substances, Clitocybine B, showed some specific action against the Koch bacillus. Such bacilli, previously brought into contact with the antibiotic substance and then transferred on suitable media, showed an extremely delayed growth. Experiments *in vivo* were carried out on guinea pigs. The animals were inoculated with tubercle bacilli and afterwards treated with daily subcutaneous injections of the extract. Circumscribed, pulmonary lesions developed with characteristic, histological features, as scant caseation, absence of epithelioid and lymphoid cells, abundance of polymuclear leucocytes. Tubercle bacilli were either completely absent or they formed agglomerated, ill defined masses. In such cases, the leucocytes also contained numerous, phagocytosed tubercle bacilli. The author concludes from these findings that the substance not only inhibits the growth but also causes lysis of the bacilli and prevents them from elaborating their cytotoxic products, so that they may be acted upon and phagocytosed by the leucocytes. The author has succeeded in culturing the mycelia on Sabouraud's media and in obtaining crystallized and more purified extracts, with which extensive experiments are now being carried out.—*La Clitocybine et le bacille tuberculeux*, C. Hollande, *Méd. Digest, Bruxelles*, No. 5, May, 1947.—(E. C. Frey)

**Tuberculin Sensitivity.**—Recently, Chase was successful in transferring tuberculin sensitivity passively by injecting cells from peritoneal exudates of tuberculin-sensitive guinea pigs into normal guinea pigs. Freund, Valtis, and Valtez and Saenz found a difference in the intensity of the tuberculin test in very young and old guinea pigs actively sensitized by infection. An attempt to duplicate Chase's studies and to determine whether the age of the animals has a pronounced influence on the passive transfer of sensitivity is reported in this paper. The method of sensitizing 22 guinea pigs approximately 132 weeks old, and 33 guinea pigs 3 weeks old and the tuberculin tests performed four weeks later are described in detail, as well as the method of obtaining peritoneal exudate cells from the animals and inoculating measured volumes of these cells peritoneally into normal animals. Twenty-four and forty-eight hours after inoculation, the recipients were tested intracutaneously with dialyzed Old Tuberculin. The skin reactions were measured twenty-four and forty-eight hours following the test injections. Control injections with the peritoneal exudates obtained from 10 young and 3 old not sensitized guinea pigs were given to 5 normal young animals, and they were tested like the experimental animals. In 3 cases slight, transient reactions to a 1:40 dilution of tuberculin were found which disappeared before the end of forty-eight hours; therefore, only forty-eight hour readings were considered reliable. Characteristic tuberculin reactions were obtained in 7 of the 10 animals which received peritoneal exudates from sensitized guinea pigs. No reactions occurred in animals treated with exudates from normal guinea pigs. Thus, the work of Chase was confirmed. However, reactions of approximately the same size were elicited in both young and old recipient animals; passive transfer of sensitivity did not appear to be greatly influenced by the age of the donor or the recipient animals.—*Passive Transfer of Tuberculin Sensitivity in the Guinea Pig*, M. M. Cummings, Martha Hoyt & R. Y.

Gottschall, *Pub. Health Rep.*, July 4, 1947, 62: 594.—(O. Pinner)

**Tuberculin Sensitivity.**—Mode of administration of tubercle bacilli as a factor in production of allergy in animals has been studied in an effort to obtain further information regarding the phenomenon of skin sensitivity to tuberculin. Bovine bacilli, Dupuy strain, of known virulence were used in doses of 0.1 mg. Tuberculin tests were made by intracutaneous injection of standard Pasteur Institute product diluted 1:10. Only animals surviving long enough for adequate testing of sensitivity were included in the report: a total of 51 guinea pigs. Subcutaneous inoculation of 15 animals resulted in the classical local lesion by the twelfth day. All reacted to tuberculin by the fifteenth day. This reaction followed the well-known process of progressively augmented intensity. The animals died by the thirty-eighth to sixty-fourth day with classical lesions. This group may be considered as controls. Only 2 guinea pigs received intramuscular injections; both had positive tuberculin reactions by the fifteenth day; both died with gross visceral lesions within two months. Twenty-four animals received intratesticular injections which produced acute orchitis within fifteen days. All died between fifteen to forty-six days with very acute peritoneal and visceral lesions. However, these animals showed no reaction to tuberculin on repeated injections between the thirteenth and thirty-seventh days. A few of these animals showed very slight thickening of the skin at the injection site, but the reaction was not considered positive. Four animals infected intratracheally died between the twenty-first and fortieth day; 3 among them had no reaction to tuberculin on the seventeenth and twenty-third days; one reacted positively on the same days. This animal had a local lesion at the site of injection. Intravenous inoculation of 6 animals with minute doses of bacilli caused death without showing any reaction to tuberculin in thirteen to twenty-eight days. Two guinea pigs infected intraperitoneally died in thirty

days with negative tuberculin reactions. This study indicated that sensitization of the skin to tuberculin results after inoculation of bacilli in the skin and muscle only. Perhaps because of the rapid progress of the disease induced by other routes of inoculation the animals lost their ability to react, although many tests were made several weeks before death with negative reactions. Apparently a tegumentary lesion plays an important role in producing allergic sensitivity when one seeks to demonstrate such allergy by cutaneous reactions.—*Influence sur l'apparition de l'allergie cutanée chez le cobaye de la voie d'inoculation de bacilles tuberculeux*, P. Gastinel & A. Nuel, *Ann. Inst. Pasteur*, May, 1947, 73: 485.—(P. Q. Edwards)

**Tuberculin Tests.**—Almost all persons giving a negative reaction to an adequate tuberculin test are free from clinical tuberculosis. Infrequently, a negative reactor may prove to be infected or rarely to be a clinical case. A few negative reactions are due to waning of skin sensitivity with passage of time in obsolete cases of infection. Nonreactors are sufficiently numerous to make the test of practical value in children and young adults.—*The Significance of the Negative Tuberculin Test*, B. Couls, *Brit. J. Tuberc.*, April, 1947, 41: 42.—(A. G. Cohen)

**Weltmann Reaction.**—The laboratory findings of 100 cases of pulmonary tuberculosis were correlated to clinical observations and course of the disease. Out of 82 cases with a slightly to moderately shortened coagulation band (Weltmann), 20 died, the remaining 62 improved. All but one of the 18 cases with elongated coagulation band became clinically arrested. The sedimentation rate was the most sensitive indicator for the degree of activity of the disease. The results of the Takata reaction were irregular and failed to show any correlation with course and clinical signs. Thus, sedimentation rate and Weltmann nephelogram are the tests best suited to assist the clinician in prognosticating pulmonary tuberculosis.—*Zur Humoralpatho-*

logic der Lungentuberkulose, A. Pedrozzi, Schuriz. Ztschr. f. Tuberk., 1947, 4: 274.—(B. Gerstl)

**Calcification and Skin Sensitivity.**—An attempt has been made to solve the etiology of pulmonary calcifications, using the subjects and data of the Fels Research Institute in southwestern Ohio. Two hundred "normal" children have been studied from birth by means of serial X-ray films (each six months for two years, yearly thereafter), and 170 have had skin tests with tuberculin, histoplasmin and other antigens. It is known that 25 to 83 per cent of young persons, living chiefly on the eastern slope of the Mississippi River basin, show calcification in X-ray films; less than half react to tuberculin, but the non-reactors are often sensitive to histoplasmin. In the present survey, the 170 children were all one year of age or older (45 were less than 5 years of age, 53 were from 5 to 9, 50 were from 10 to 14, and 22 were from 15 to 19 years). The skin-test routine consisted of the usual two strengths of PPD, a single dose of 1:1,000 histoplasmin, and, if these were all negative, tests with 1:1,000 blastomycin and haplosporagin. One hundred and three children (60.6 per cent) showed intrathoracic calcification. Tuberculin tests were positive in 15.3 per cent of the entire group; histoplasmin tests were positive in 44.7 per cent. Eighteen children reacted to both tests, 15 having calcifications; 8 reacted only to tuberculin, 6 having calcifications; 58 reacted only to histoplasmin, 49 having calcifications; 86 were negative to both, but 33 had calcifications. Of the 33 children negative to the routine tests, only 2 reacted to blastomycin, and one of these also reacted to haplosporagin. Previous tuberculin tests indicate that the positives and negatives have remained constant in spite of the presence of calcification. The study has allowed X-ray and skin-test surveys of relatives of the children; there has been a tendency to family distribution of calcification, but not of histoplasmin sensitivity. In summary, more children were sensitive to histoplasmin than tuberculin;

the incidence of pulmonary calcification is more closely associated with histoplasmin sensitivity than tuberculin reaction; and there is a much closer association between the onset of calcification and histoplasmin sensitivity than with tuberculin sensitivity. Most of the children with calcifications showed soft tissue changes by roentgenogram before 48 months of age, consisting of infiltrates and round areas of consolidation. New lesions continued to appear and calcify in children with positive histoplasmin tests.—*Lung Calcifications and Histoplasmin-Tuberculin Skin Sensitivity*, L. W. Sontag & J. E. Allen, *J. Pediat.*, June, 1947, 30: 657.—(W. H. Oatway, Jr.)

**Inhibition of Mycobacterium.**—The author added varying concentrations of monoalkyl and dialkyl succinic acids and monoesters and monoamido-derivatives of alkyl succinic acids to a nutrient peptone digest broth which in some cases was enriched with 5 per cent pooled human serum. The medium was inoculated with either *M. smegmatis*, *M. tuberculosis bovis* 46 or *M. tuberculosis hominis* H37RV. Final readings of the growth of *M. smegmatis* were taken on the sixth day and of *M. tuberculosis bovis* or *hominis* on the forty-second day of incubation and compared with the controls. The chemicals were also tested for hemolytic action on standard suspensions of washed human erythrocytes at 37° C. for one hour. It is concluded that some of the new series of compounds markedly inhibit the growth of *M. tuberculosis*. The antibacterial and hemolytic action was most marked when the combined constituents of the compounds contain 13 or 14 carbon atoms. The antibacterial action is bactericidal. The addition of serum albumin to the compounds reduces the antibacterial and hemolytic action.—*The Action of Monoalkyl and Dialkyl Succinic Acids and the Monoesters and Monoamido-Derivatives of Alkyl Succinic Acids on the Growth of Mycobacterium Tuberculosis*, P. A. McNally, *Brit. J. Exper. Path.*, June, 1947, 28: 211.—(H. J. Henderson)

**Friedmann's Vaccine in Genital Tuberculosis.**—A 16-year-old girl was operated upon for tuberculous oophoro-salpingitis and afterwards received one dose of Friedmann's vaccine subcutaneously. This seemed to result in immediate and visible improvement of her general and local conditions. However, two months later she lost weight rapidly and experienced severe pain in her left lung. A soft infiltration was found in the left infraclavicular and basal regions and collapse therapy was started. The author points out that all surgical localizations of tuberculosis are secondary to a pulmonary lesion, sometimes undetectable in its beginnings. The follow-up of gynecological cases of tuberculosis treated with Friedmann's vaccine has not shown sufficient success to warrant the enthusiasm of certain gynecologists for his treatment. [It would seem that the inefficacy of treatment with Friedmann's vaccine was well established a good many years ago. —Editor]—*A proposito de un caso de tuberculosis genital tratada con vacuna a germenes vivos, R. Burgos, Hoja fisiol., December, 1946, 6: 477.*—(W. Sixtenty)

**BCG Vaccination.**—This is an evaluation of present data on the efficacy of BCG in the prevention of tuberculosis. The safety of BCG in man is accepted on the basis of the experience with over 5,000,000 inoculations. However, there are numerous favorable reports on the efficacy of BCG vaccine taken severely to task, because many of them have been inadequately controlled. This criticism certainly does not apply to the work of Aronson on the protection of American Indians by BCG. Practically all the criteria set down by Levine for a searching investigation into the efficiency of the vaccine have been scrupulously fulfilled by Aronson and his associates, including the all important alternating of individuals for vaccination and control. Unfortunately, Levine is under the misapprehension that this was not done in the Indian study. Levine has been influenced in his skepticism on efficiency of BCG by the absence of decisive data in his own experience in

New York. Whether this is due to the very low incidence of tuberculosis among these children and hence, under the circumstances, to a very limited experience, remains to be determined. Despite these criticisms, which in some instances are well taken, Levine concedes that the BCG affords a certain degree of protection. He therefore urges continued research in BCG vaccination, especially in relation to the duration of the immunity afforded, the significance of tuberculin sensitivity following vaccination, the efficacy of the vaccine in different racial groups and the relative potency of the BCG when prepared under different conditions.—*An Evaluation of the Use of BCG in the Prevention of Tuberculosis in Infants and Children, M. I. Levine, Am. J. Pub. Health, September, 1947, 37: 1096.*—(M. B. Lurie)

**BCG Vaccination.**—In a rather long address at Brussels on December 5, 1946, before the Belgian Society for the Scientific Study of Tuberculosis and Pneumology, Guérin, co-worker of Calmette in the development of BCG, summarizes his views of the value of his vaccine. If postnatal exposure takes place within the first three months of life, the mortality is nearly 100 per cent; if within the first year and one-half, 30 per cent. As children become older their resistance to tuberculosis increases for two reasons: their bodies have developed greater natural resistance and they have acquired a degree of specific resistance through occasional contact with tubercle bacilli not too numerous or too virulent. Many persons do not come in contact with tubercle bacilli and secure spontaneous resistance until adolescence. This is particularly true of children who grow up in the country and later come to the city to work. Recruits for the Army from the country are in the same category. Many of these persons are as readily infected as infants, and have as a result of this infection a rapidly progressive form of tuberculosis. The one means that, according to the present state of our knowledge, has proven of value is the introduction into the body of living tubercle bacilli, which

however should have no power of doing harm to the individual who receives them. The Pasteur Institute at Lille had in 1908 a strain of tubercle bacilli of marked virulence. Calmette and Guérin cultured it on strongly alkaline glycerinated-bile potato medium and made transplants every fifteen days. It became less and less virulent and after thirteen years, that is after 230 transplantations, it had lost all capacity of provoking the formation of reinoculable tubercles. After tests on some hundreds of thousands of young calves and other animals, it was found that it had retained its power of vaccinating against later infections with virulent tubercle bacilli. Vaccination with BCG was first applied to human beings in 1921. Since that time, according to Guérin, over a million individuals have been vaccinated in France and many thousands elsewhere. Twenty-five years have passed and it is now possible to assert that it is not at all dangerous and that it is effective. The technique of vaccination by scarification, which is similar to that of smallpox vaccination, has come into wide use and is given in some detail. BCG is an attenuated strain of tubercle bacilli which has become stabilized and which will not produce progressive disease. It may therefore, if properly administered, be considered harmless. This paper by one of the originators of BCG vaccination is interesting and well worth reading.—*La vaccination par le B.C.G., C. Guérin, Rev. belge de la tuberc., 1947, 38: 1.*—(A. T. Laird)

**Electrokymography.**—Roentgen kymography was invented by Sabat in 1911. This procedure is the roentgen demonstration of the movements of the diaphragm, heart and aorta. The apparatus was simple, consisting of a single slit diaphragm. In 1928, Stumpf introduced the grid with multiple parallel slits replacing the diaphragm. Hirsh, in 1934, devised a system permitting synchronization of the kymographic tracing with the electrocardiographic tracing. In 1942, Morgan invented the phototimer, a remarkable instrument capable of automatically controlling the time of exposure in reontgenography under

various conditions. Chamberlain, Henny and Boone combined the photoelectric pick-up of heart movements with an electrocardiographic type of registration to make a new instrument, the roentgen electrokymograph. This instrument has obvious technical advantages over ordinary roentgen kymography. It will soon prove its usefulness in the examination of many hitherto undiagnosable conditions of the cardiovascular system.—*Roentgen Kymography and Roentgen Electro-kymography, T. Leucutia, Editorial, Am. J. Roentgenol., May, 1947, 57: 629.*—(J. E. Farber)

**Breath-holding Time.**—In 341 determinations with the subjects at rest at ground level (altitude 500 feet) breathing air, the breath-holding time was 34 to 125 seconds, with an average of seventy seconds. Hyperventilation and oxygen inhalation increase the breath-holding time. It decreased with increasing altitude and following exercise. The average breath-holding time during escape from a spinning centrifuge, imitating the conditions of spinning aircraft, was seventeen seconds.—*The Effect of Oxygen, Altitude and Exercise on Breath-Holding Time, S. Rodbard, Am. J. Physiol., July, 1947, 150: 142.*—(G. C. Leiner)

**Respiratory Volumes of Laboratory Animals.**—Several methods of determining the respiratory volume, including the oscillographic respiograph, have been presented. Data on quiet respiration in 428 animals of 8 species have been presented. The data presented indicate that the respiratory volume varies directly neither with the weight of the body nor with the body surface but approximately with the  $\frac{2}{3}$  power of the weight. A formula has been derived for the determination of respiratory volume of an animal provided the weight is known. (Author's Summary.)—*Measurement of the Respiratory Volumes of Laboratory Animals, A. C. Guyton, Am. J. Physiol., July, 1947, 150: 70.*—(G. C. Leiner)

**Respiratory Patterns in Laboratory Animals.**—Respiratory patterns of mice, cotton

rats, hamsters, white rats, guinea pigs, rabbits, monkeys, dogs and men have been illustrated and analyzed. In general, the respiratory pattern varies little between one species of animals and another except for rate and tidal air. Within any one species of the smaller animals, the respiratory pattern is relatively constant. Formulae based on weight have been derived for tidal air, rate of breathing, inspiratory and expiratory rate of flow, inspiratory and expiratory speed of flow, pressure drop in the trachea, and retention of particles within the nasal passages. In general, the calculated values from these formulae agreed within 20 per cent of those which could be measured. Considering the great number of variables in respiratory dynamics, this agreement is considered to be reasonable. As an example of information which can be gained from respiratory patterns, two experiments on the anesthetization of rabbits with nembutal are presented. (Author's Summary.)—*Analysis of Respiratory Patterns in Laboratory Animals*, A. C. Guyton, *Am. J. Physiol.*, July, 1947, 150: 78.—(G. C. Leiner)

**Absorption from Pulmonary Alveoli.**—Any material absorbed from a normal lung alveolus must pass through its epithelial lining and penetrate the walls of the alveolar blood and lymph capillaries. From the small surface area available and the anatomical barriers imposed, bronchiolar absorption is of little importance compared with the absorption from the alveoli. Experiments were done on dogs, anesthetized with nembutal, in which lung lymph, thoracic duct lymph, and blood specimens were separately collected after intratracheal introduction of the test materials. Nearly all the lymph from a dog's lung enters the blood through the right lymphatic duct. Despite the fact that connections between this duct and the thoracic duct are frequent, in a certain number of animals the right lymphatic duct can be individually cannulated and will deliver no lymph save from the heart and lungs. The presence of the test material in the blood

(and thoracic duct lymph) would be an indication of alveolar blood capillary absorption. The instillation of a 1 per cent solution of T-1824 (a blue dye) in physiological salt solution introduced into the trachea of a dog showed a fairly rapid appearance of the dye in the lung lymph and the blood. As there was no possibility of lymphatic delivery of dye into the blood, molecules of the dye must have directly entered the blood. In contrast to the ready absorption of T-1824 in water, certain experiments were done in which the dye was combined with proteins such as dog plasma and crystallized egg albumen. The absorption of these proteins was slight. Also purified bovine serum albumen was tested and examined by a precipitation method. Its absorption was also slight. When hemoglobin was introduced into the trachea its absorption could not be detected. Experiments in which pyrex glass spheres averaging 4 micra in diameter were instilled failed to disclose entrance of these distinctive foreign particles in the lymph stream during the test flow of lung lymph. Intact alveolar epithelium apparently permits only very slight absorption of proteins commonly entering the pulmonary alveoli as a result of trauma or disease. (With 1 plate.)—*Absorption from the Pulmonary Alveoli*, C. K. Drinker & E. Hardenbergh, *J. Exper. Med.*, July, 1947, 86: 7.—(J. S. Woolley)

**Pulmonary Function for Silicosis.**—The author calls attention to the discrepancy of roentgenographic appearance of pulmonary silicosis and the results of pulmonary function tests. Frequently, patients showing slight fibrosis and nodulation reveal severe damage on function tests, while others with advanced changes on X-ray examination show a function better than expected. The former may be due to bronchial spasms, superimposed infection, cardiovascular diseases or aggravation. The latter may be explained on the basis of adjustment to the gradually developing reduction of respiratory epithelium. Simple function tests, such as spirometry, expansion of thorax and voluntary inspiratory and expiratory apnea are considered sufficient.—*Die*

*Leistungsprüfung bei der Beurteilung von Silikotikern, F. Lang, Schweiz. Ztschr. f. Tuberk., 1947, 4: 257.—(B. Gerstl)*

**Calculation of Dead Space.**—The dead space was calculated according to Rossier's formula

$$DS = \frac{\text{Minute volume in cc.} - \text{alveolar ventilation in cc./Frequency of respiration per minute}}{\text{per minute}}$$

with and without adding an artificial dead space of 100 cc. It averaged 173.7 cc. The maximum deviation from the added 100 cc. dead space were -33 and +41 cc. The fact that a hyperventilation of +21 per cent, in presence of the artificially superimposed dead space, did not increase alveolar ventilation nor produce alkalosis of the arterial blood, suggests that the increase of minute volume is due to hyperventilation of the dead space. This hyperventilation can be prevented by bandaging the thorax tightly. It resulted in increased carbon dioxide tension of the arterial plasma, slight acidosis and a 16 per cent decrease of alveolar ventilation. The condition simulated that observed in cases of emphysema with rigid thorax, pulmonary tuberculosis, etc. The magnitude of the physiological dead space was conversely proportional to frequency of respiration, and directly proportional to respiratory volume. The dead space can be calculated according to Rossier's formula from frequency of respirations and minute volume, only if the alveolar ventilation is assumed to be constant. The correctness of this assumption is tested by determining carbon dioxide and oxygen in the arterial blood. The combination of such procedures with spirometry is therefore essential for estimating the physiological dead space.—*Totraum und Totraum-hyperventilation, E. Blickenstorfer, Schweiz. Ztschr. f. Tuberk., 1947, 4: 59.—(B. Gerstl)*

**Pulmonary Insufficiency and Oxygen Deficit.**—A double spirometer was devised permitting instant switching from pure oxygen to air containing various but constant concentrations of oxygen. Registration on the kymograph was synchronized with each spirometer and could

be continued for fifteen minutes. The minute volume was calculated from the diagrams obtained. Arterial blood samples were analyzed for oxygen and carbon dioxide. The additional uptake of oxygen upon breathing pure oxygen was small and dyspneic patients varied in their mean respiration. These factors rendered interpretation of the kymographic charts difficult. Some of the patients with respiratory insufficiency did take up additional oxygen under oxygen respiration but there was no correlation between the oxygen deficit of arterial blood and the amount of additional oxygen absorbed, or the minute volume. The quantity of oxygen taken up by normal individuals remained constant whether air or oxygen was breathed. Thus, spirometry cannot replace the determination of oxygen of the arterial blood. The large differences of oxygen uptake by cases with pulmonary insufficiency remain unexplained.—*Über das sogenannte Sauerstoff-Defizit nach Uhlenbruch-Knipping, G. Nager, Schweiz. Ztschr. f. Tuberk., 1947, 4: 1.—(B. Gerstl)*

**New Resuscitator.**—The terms used in America and England to describe treatment for asphyxia are defined. The two general types of resuscitation are discussed, the *manual* methods, requiring no equipment, and including mouth-to-mouth insufflation and the various posture and manipulation procedures, and the *mechanical equipment* methods, including transpharyngeal insufflators, endotracheal insufflators, inhalators, extrapulmonary differential pressure devices, positive-negative pressure devices, the intermittent positive-pressure devices and the rocking table. Simplicity and the use of oxygen are points favorable to a method; reliance on the elastic recoil of the chest, and the use of negative pressure intratracheally are disadvantages. The Burns PBR (Pneumatic Balance Resuscitator), or the "baby lung," is a new type of intermittent positive-pressure apparatus. The PBR valve was designed at the Aero Medical Laboratory, Wright Field. The equipment consists of a mask and an automatic valve through which the oxygen supply flows from a regulator and



source of supply. Any type of closely-fitting mask may be used. The valve contains channels and diaphragms, which allow the valve to "cycle" between the pressure in the mask and the pressure of the oxygen regulator. A rising line-pressure will close the valve; a rising mask-pressure will open the exit ports to the outside. Use of the PBR on subjects in deep coma and freshly dead is reported, as well as the effects of PBR on pulmonary ventilation, blood gas and pH content in a series of patients. The valve works well over long periods of time and in spite of secretions. PBR failed in its original purpose in aircraft, but it has several interesting clinical uses. It has been used to shorten the period of unconsciousness after general anesthesia; in narcotic intoxication with a low respiratory rate; and as an adjunct to a Drinker respirator in case of power failure or during transfer. It may also be of value in cases of cardiac failure, since use of the valve results in a decreased venous return to the heart—a result similar to that of venesection and peripheral tourniquets. PBR may be of considerable use to the clinician.—*Artificial Respiration and the Pneumatic Balance Resuscitator*, H. J. Jacobs, *Bull. U. S. Army M. Dept.*, August, 1947, 7: 707.—(W. H. Oatway, Jr.)

**Interlobar Fissures.**—Variations of interlobar fissures of the lungs were studied in 1,200 consecutive autopsies. A complete fissure was found in 82 per cent in the left lungs, a major fissure in 70 per cent in the right lungs and a middle lobe fissure in 38 per cent in the right lung.—*Variations in Interlobar Fissures*, E. M. Medlar, *Am. J. Roentgenol.*, June, 1947, 57: 723.—(J. E. Farber)

**Agenesis of Lung.**—The term "agenesis" should be restricted to those cases with no development of the lung, and "aplasia" should be used for those with incomplete development (as suggested by Schneider). Since the advent of bronchoscopy, the diagnosis is made more often in living patients. A total of 54 cases have previously been reported, to which one case is added. A Negro infant, aged 2 months,

was admitted to the hospital in respiratory distress and in poor general condition. There was consolidation, lack of aeration and narrowed interspaces on the left. Death occurred in twenty-four hours. Necropsy showed agenesis of the left lung; agenesis of the apical lobe and eparterial bronchus on the right; absence of the left pulmonary artery; edema and congestion of the right middle lobe; atelectasis of the right lower lobe; a patent ductus arteriosus and foramen ovale; cor pulmonale, and displacement of the heart to the left; and an inguinal hernia on the left. The embryology and diagnosis are discussed, and 11 recent cases are tabulated.—*Agenesis of the Lung: With a Review of the Literature*, R. A. Burger, *Am. J. Dis. Child.*, April, 1947, 73: 451.—(W. H. Oatway, Jr.)

**Spontaneous Pneumothorax in Sarcoidosis.**—A case of sarcoidosis verified by biopsy in which a spontaneous pneumothorax occurred is reported. The course of the disease remained benign and the pneumothorax was resorbed without further therapy.—*Spontanpneumothorax bei der Besnier-Boeck-Schaumann'schen Krankheit*, M. Dressler, *Schweiz. Ztschr. f. Tuberk.*, 1947, 4: 229.—(B. Gerstl)

**Carcinoma of Lung.**—Symptoms and signs of carcinoma of the lung depend upon the relationship of the growth to the thoracic organs, particularly the pressure effects upon the lung and bronchi. Complete obstruction of the large bronchi, usually by squamous cell carcinoma, results in atelectasis. Incomplete obstruction results in suppuration with or without lung abscess. There may also be breakdown within the tumor itself, in which case the abscess is not segmental, is radiologically eccentric to the main shadow and may have an irregular outline. Invasion of the pleura results in pain or discomfort and effusion. The fluid may be clear, bloody or purulent and may or may not contain tumor cells. Interference with the mediastinal tissue is due to glandular involvement; this is seen in the oat cell or undifferentiated types. The great veins may be obstructed and there may be paralysis of the

phrenic or recurrent laryngeal nerves. The heart is invaded sometimes. Glandular metastases are common in the oat cell type where the lymph nodes are heavily involved; surgery is impracticable in these cases. Regional metastases are less common in squamous cell and adenocarcinoma. In these, secondary deposits may develop with predilection for bone (ribs and vertebrae), liver, skin, brain and adrenals. The early symptoms of significance are: (1) appearance or change in the character of the cough in middle-aged or older persons, (2) hemoptysis and (3) dyspnea and transitory wheezing. Pleuritic pain and osteoarthropathy are also significant. The most important diagnostic procedures are X-ray, bronchoscopy and identification of cancer cells in the sputum. Oat cell carcinomata with regional metastases are inoperable. Squamous cell carcinomata giving early atelectasis are often removable. Pleural effusion, glandular involvement, infiltration of the phrenic and vagus nerves and extension to the diaphragm or chest wall, while not absolute contraindications, make success doubtful. The proportion of suitable cases is very low. In the authors' series the chest was opened in 246 cases; resection was possible in 130 (122 pneumonectomies and 8 lobectomies). There were operative deaths in 15 per cent. Postoperatively the most important consideration was the behavior of the vacant space. If no infection occurred, there was slow obliteration in a few months with increasing deposit of fibrin. Some patients later required a thoracoplasty.—*Carcinoma of the Lung*, T. H. Sellors, G. Cruickshank & B. R. Billimoria, *Lancet*, July 26, 1947, 2: 119.—(A. G. Cohen)

**Resection for Neoplasm of Lung.**—A detailed analysis has been made of the fate of 360 patients with primary pulmonary malignancy seen in the eleven years between January, 1936 and December, 1946. Twenty-eight per cent occurred in private practice, 16 per cent of which came to pulmonary resection; 72 per cent were seen in a charity hospital, 43 per cent of which had resection—a total of 129 resections. Compared with the stable occurrence

of carcinoma of the stomach, there seems to be a slight yearly increase in the incidence of primary carcinoma of the lung. No reason (such as occupation or smoking) was found for this increase. The condition is twice as common in whites as in Negroes, and more than four-fifths of all patients were males. By far the greatest number were between 40 and 70 years of age, with the greatest incidence in the fifth decade. The insidious onset and the vague clinical picture account for the frequent delay in diagnosis. The common sites of involvement have been listed, but the pathology is to be reported later. The mortality without surgery is considered to be 100 per cent. Of the 360 cases, 109 were considered to be inoperable and 41 refused surgery—a total of 150 (42 per cent); 251 (70 per cent) were considered operable, and 210 were explored; 81 cases (22 per cent) were nonresectable, and 129 cases (36 per cent) were resected. Fourteen of those explored but not resected died in the hospital; 32 of those resected (24.8 per cent) died in the hospital. Forty-five patients were alive from six months to five years after resection—a range of 54 to 22 per cent of those resected. A person who lives three years after resection usually is alive at five years. Extensive charts are shown to illustrate the various rates and their modifying factors. It is suggested that routine roentgenological examination of the chest is the most valuable diagnostic method. It should be supplemented where indicated by bronchography, bronchoscopy, biopsy and study of bronchial secretions.—*Primary Pulmonary Malignancy Treated by Resection*, A. Ochsner, M. de Bakey & L. Dixon, *Ann. Surg.*, May, 1947, 125: 522.—(W. H. Oatway, Jr.)

**Surgery for Carcinoma of Lung.**—The first pneumonectomy was done thirteen years ago at Johns Hopkins Hospital. Diagnosis of primary pulmonary carcinoma was rare at that time. Medical and radiation therapy was and is ineffective. A series of 327 consecutive cases seen during the thirteen years is presented, and the data are analyzed. The majority of patients is in the fourth to sixth decades. A high proportion (6 to 1) were

males, a possible result of the exposure of that sex to chronic irritations of the lungs and its resultant stimulation of abnormal cell growth. There are no pathognomonic signs or symptoms, but an unusual and persistent cough or an unexplained hemoptysis is suggestive. The X-ray film showed lesions in 100 per cent of the cases. Exploratory thoracotomy is the final diagnostic method, and should be used more freely. The majority of the cases in this series were near the hilum; they either arose from the mucosa and grew into the bronchus (centripetally), or arose from a small bronchus and grew extrabronchially along or around the bronchus. The symptoms depend considerably on the method of growth. Sixty-five per cent were flat, or squamous cell carcinomata; 35 per cent were adenocarcinomata. In general, the patients with squamous cell type lived longer after excision. A total of 215 cases (66 per cent) was inoperable, by reason of pleural or distant metastases. Pneumonec-tomy was the only type of operation used, and it was done in 112 cases. Seventy per cent had metastases in the bronchial or tracheobronchial nodes. The preoperative preparation, using penicillin and pneumothorax, is described, as is the operative procedure. The immediate postoperative mortality, including all deaths during the first month, has been 22 per cent (27 per cent from 1933 through 1939, 17 per cent from 1940 through half of 1946). Forty-four cases (39 per cent of those resected) survived the operative period but are now dead. Forty-three cases (39 per cent of those resected, 13 per cent of the entire series) have lived from one month to thirteen years. The average duration of life of the 215 cases which were nonoperable was five months. Most patients have been rehabilitated to their usual work and recreation. It has rarely been necessary to do a thoracoplasty.—*The Present Status of the Surgical Treatment of Carcinoma of the Lung*, W. F. Richhoff, *Ann. Surg.*, May, 1947, 125: 541. —(W. H. Oatway, Jr.)

**Cancer of Lung.**—Cancer of the lung seems to be on the increase everywhere, and it is thirteen years since the first patient was success-

fully operated. This report deals with 280 cases, histologically verified, 51 per cent of which were operated. By sex, 220 were men and 60 women. The age varied from 18 to 77 years. Cough was the symptom which made the patient seek medical advice in 87 per cent. Fever was present in 54 per cent of those with secondary infection, pain in the chest in 49 per cent, hemoptysis in 43 per cent, dyspnea and wheezing in 30 per cent. No symptom or complex may be called truly typical. In 65 per cent the condition was masked by other possibilities, it having been diagnosed as tuberculosis (21.2 per cent), pneumonia (11.1 per cent), bronchitis (10.4 per cent), abscess of the lung (5 per cent), bronchial asthma (4.6 per cent), heart disease and pleurisy (3.6 per cent each), and so on. On an average, symptoms had been present for 3.7 months before seeing a physician, for six months before an X-ray was taken, and for 11.3 months before the diagnosis was made. X-ray changes are too variable to be conclusive. Bronchoscopy was performed in 251 cases and in 171 the accompanying biopsy settled the diagnosis. In the first five years of this study biopsies proved positive in 75 per cent, while in the second five years the figures have come down to 53 per cent. In other words, the earlier the biopsy, the more difficult it is to secure diseased tissue for examination. In 204 patients (75 per cent) the disease originated in one of the main bronchial tubes and in the rest in the smaller tubes. These latter cases are the ones in which bronchoscopy naturally fails. Conforming to the pattern in tuberculosis, the upper right lobe is the one most frequently affected (26 per cent), the upper left lobe coming next (18.3 per cent). Next to bronchoscopy, an exploratory thoracotomy (74 cases) or a biopsy of metastases (22 cases) proved to be the most reliable verification. Out of 275 cases diagnosed during life, 129 were found inoperable and 4 declined the operation. Radiotherapy is mentioned only to deplore the time it makes the patient lose in securing proper surgical treatment. In 7 cases the lesion was detected before symptoms developed, and in all but one this permitted removing the lung before metastases occurred

in regional nodes. The operations included 73 exploratory thoracotomies, 27 palliative pneumonectomies, 40 curative pneumonectomies and 7 lobectomies. The operative mortality in the 74 excisions was 19.7 per cent for the whole period, but it decreased from 33.3 per cent in 1933-1936 to 9.8 per cent in 1940-1945. The lobectomies were made during the earlier period and proved too conservative. Living patients without metastases total 25 (7.5 per cent of 280 patients, and 52.5 per cent of 47 excisions). Five-year cures represent 1.5 per cent of the total series and 10.5 per cent of the 47 radically operated. (This study was made at the New England Deaconess Hospital in Boston.)—*Carcinome broncogénico: Estudio clínico y resultado del tratamiento quirúrgico en 280 casos*, L. Langer, *Prensa med. argent.*, May 23, 1947, 34: 932.—(A. A. Moll)

**Induction of Bronchogenic Carcinoma in Mice.**—Bronchogenic carcinomata were induced in mice from subcutaneous grafts of adult lung tissue impregnated with 2: methylcholanthrene. In mice of strain C3H, the tumor incidence was increased if the lung grafts were impregnated with stilbesterol in addition to the carcinogen. Histologically, the tumors were bronchogenic.—*Induction of Bronchogenic Carcinomas in Mice*, E. S. Horning, *Lancet*, August 9, 1947, 2: 207.—(A. G. Cohen)

**Bronchogenic Carcinoma.**—Thirty-six autopsied cases of bronchogenic carcinoma, observed between 1937 and 1945, were studied. These comprised approximately 8.6 per cent of all autopsies performed during this period at the Brooklyn Cancer Institute. Thirty-two, 88 per cent, were males. The mean age was 55.1 years; this is significantly lower than the mean age of many common malignancies. Nonproductive cough is the earliest and most common symptom. Bronchoscopic diagnosis is possible in the early stage when physical examination and X-ray examination are often negative. The development of asthmatic breathing in middle-aged individuals should arouse suspicion of a pulmonary carcinoma.

Secondary infection behind the tumor is frequent. When a portion of the obstructing tumor breaks down, the infection may subside temporarily. Atelectasis is frequent and is almost always associated with infection. Fever is often present and may lead to an erroneous diagnosis of pneumonia. Metastatic deposits are not infrequently the first clinical manifestation of bronchogenic malignancy; this is particularly important in cerebral metastases which may be mistaken for primary brain tumors. Cerebral metastases were found in 7 cases. Metastases occurred most frequently to the thoracic lymph nodes, the other lung, the liver, bones, adrenals and kidneys. The bones most commonly involved were the vertebrae, pelvis and femora. The mean and median life expectancies were eight months from onset of symptoms. All were dead within twenty-eight months. Interval X-ray study of a suspicious lesion is not justified. Roentgen therapy is indicated for palliation. Response to X-ray therapy cannot be predicted on the basis of cellular type. The carcinocidal dose is probably above 5,000 roentgens. There was no relation between administered tumor dose and longevity.—*Bronchogenic Carcinoma: A Clinical Pathological Study of 36 Autopsied Cases Seen at the Brooklyn Cancer Institute between 1937 and 1945 inclusive*, W. H. Henkin, *Ann. Int. Med.*, August, 1947, 27: 243.—(H. R. Nayer)

**Intrabronchial Cancer Metastasis.**—In a series of 1,200 cases of primary and secondary pulmonary cancer, 8 cases of intrabronchial metastases were found. Histologically, they were adenocarcinomata and assumed to be metastatic in origin. There was no true bronchogenic spread.—*Untersuchungen über Krebsmetastasen*, H. Walther, *Schweiz. Ztschr. f. Tuberk.*, 1947, 4: 319.—(B. Gerstl)

**Surgical Resection for Metastatic Neoplasm.**—The appearance of a solitary metastatic lesion in a lung months or years after the removal of a primary extrapulmonary sarcoma or carcinoma is not rare. Previously, there were 5 reported cases in which pulmonary re-

section had been done for this type of lesion; to these, the authors now add 19 of their own. Of the 24 cases, there was one operative death and recurrences in 11. Of the other 12, 8 are well twelve years to one year postoperatively; 4 were operated upon only recently. Six of 8 sarcomata and 6 of 15 carcinomata are apparently well. The operation was either lobectomy or pneumonectomy.—*Pulmonary Resection for Solitary Metastatic Sarcomas and Carcinomas*, J. Alexander & C. Haight, *Surg., Gynec. & Obst.*, August, 1947, 85: 129.—(A. G. Cohen)

**Chest Injuries.**—Injuries of the chest are responsible for about 25 per cent of battlefield deaths. In these cases roentgenoscopy is of value in the study of foreign bodies, fluid levels and lung reëxpansion, in observing diaphragmatic mobility and thoracic cage motion, in detecting pleural fluid and adhesions, in studying heart configuration and motion. Traumatic conditions described include: pulmonary contusion and hematoma, simple, loculated and clotted hemothoraces, atelectasis, blast injury, bronchopleural fistula, missile tracks, transdiaphragmatic and bony thorax injuries and subcutaneous emphysema.—*Roentgenological Aspects of Battle Injuries of the Chest*, Major M. Rakofsky & Capt. V. P. Satinsky, *Am. J. Roentgenol.*, May, 1947, 57: 588.—(J. E. Farber)

**Tropical Eosinophilia.**—This syndrome was first described by Frimodt-Møller and Barton (1940) in southern India. Weingarten (1943) discovered that a short course of neoarsphenamine produced dramatic improvement. While tropical eosinophilia is not a rare disease in India and Ceylon, its existence in Africa has not as yet been generally recognized. The present study was carried out in Dar-es-Salaam, Tanganyika. Differential white counts were performed on a consecutive series of 34 male patients with symptoms of recurrent bronchitis or asthma. Eosinophilia of less than 20 per cent was found in 28 cases. In the 6 cases remaining, eosinophilia of 40 to 80 per cent was present. An additional seventh

case was referred because of an unexplained eosinophilia. Six were treated successfully with arsenic, while the condition regressed spontaneously in the seventh. Clinical findings were recurrent attacks of cough, wheezing, low fever, with asymptomatic intervals except for episodes of spasmodic coughing in the early morning. After a variable number of attacks, the interval of freedom became shorter, and cough and dyspnea caused increasing distress. Patients with long-standing illness complained of lassitude, anorexia and loss of weight. Three cases had no abnormal X-ray findings, while 3 had a mottled X-ray appearance. Red counts varied between 4,650,000 and 5,150,000, with hemoglobin from 94 per cent to 110 per cent, comparatively high for a country where anemia is prevalent. Leucocytosis varied from 11,250 to 34,000, with an eosinophilia of 52 to 78 per cent. The eosinophils often contained vacuoles. These disappeared in the course of treatment. Sputum for tubercle bacilli was negative. Four mites of *Tyroglyphus* and a few ova were found in specimens from case II, one mite of *Tyroglyphus* in case VI, and an unidentified mite in sputum from case IV. No mites were found in sputum from cases III and V. Löffler described a syndrome characterized by fever, cough and eosinophilia, with positive X-ray findings and rapid spontaneous recovery. It is unlikely that this is similar to tropical eosinophilia, which has had a known duration of as long as three years. Some think that tropical eosinophilia is an atypical form of asthma. However, the presence of fever, leucocytosis, splenomegaly and characteristic shadows in the X-ray of the chest would seem to differentiate it from Löffler's syndrome. Because of its close resemblance to infectious mononucleosis, the theory that it is a specific infection is favored, and, because of the presence of mites in the sputum, it is assumed that they are a direct or indirect cause of the disease. A similar condition has been reproduced in monkeys by the introduction of ova into the trachea. Treatment with inorganic arsenic is dramatically successful. The most effective method appears to be a ten-day course of carbarsone, followed

after a few days by four weekly injections of neoarsphenamine (0.6 to 0.75 g.).—*Tropical Eosinophilia in East Africa*, H. T. H. Wilson, *Brit. M. J.*, June 7, 1947, 4509: 801.—(R. W. Clarke)

**Benign Recurrent Meningitis.**—The question raised in 1943 by the writer when reporting the first case of a peculiar mild recurrent lymphocytic meningitis is restated. Is it a new condition? The distinguishing and most interesting feature is its recurrent character and prompt subsidence. Mollaret reported (1944) 4 cases seen since 1928. Onset is sudden, usually in the afternoon, with fever, aching pains and meningeal signs, vasomotor disturbances and occasional vomiting and epileptic-like seizures. The attacks, which last twenty-four to forty-eight hours, continue for several years, at first every two or three months, and then once or twice every month. Finally, intervals between attacks lengthen until they cease completely. Spinal fluid is cloudy, opalescent and shows no pus, fibrin or tension, with preponderance of lymphocytes among cells present. Asthmatic episodes occurred between attacks. Discrete X-ray signs in the chest in 3 cases suggested a tuberculous allergy. Only the study of new cases can clarify the true nature and etiology of the condition.—*La meningitis multirrecurrente benigna, enfermedad nueva?*, J. Calvo Melendro, *Bol. Inst. de pat. méd.*, Madrid, March, 1947, 2: 45.—(A. A. Moll)

**Portland Cement Dust.**—The hypothesis that exposure to high concentrations of industrial dusts may lower resistance to acute pulmonary infections was investigated. In this paper, the effect of inhalation of cement dust on the resistance of rats to lobar pneumonia was studied. Portland cement contains less than one per cent of free silica. The animals were exposed for varying periods of time, two days to thirty weeks, to air containing the dust with an average of 200 million particles per cubic foot; 80 per cent of the particles were 3 micra or less in diameter. Intrabronchial inoculation with type one pneumococci was

then carried out. Control animals were used throughout and over one thousand rats were employed in the experiment. Resistance to lobar pneumonia was not lowered by exposure to the dust. Microscopic examination of the lungs of the exposed animals did not reveal any acute or chronic changes which could be ascribed to the dust. Petrographic studies indicated the progressive solution of the cement particles in the lungs without any resulting fibrosis.—*Effect of Portland Cement on the Lungs with Special Reference to Susceptibility to Lobar Pneumonia*, Anna M. Baetjer, *J. Indust. Hyg. & Toxicol.*, July, 1947, 29: 250.—(H. R. Nayer)

**Bronchiectasis.**—Nebulization therapy was used for 86 patients with chronic bronchiectasis. Forty-six patients were treated in preparation for excisional surgery, 40 patients were not suitable for surgical intervention. In all 86 patients penicillin aerosol was used, in 27 patients streptomycin hydrochloride was added to the penicillin solution for nebulization. In the latter group a combination of 200,000 units of penicillin with 0.5 to 1.0 g. of streptomycin dissolved in 20 to 30 cc. of isotonic sodium chloride solution was used for daily nebulization. In the majority of the surgical cases the volume of pulmonary secretions was reduced considerably in the preoperative period. The nonsurgical group was treated from two to eight weeks. The treatment was considered satisfactory if the daily volume of purulent secretions was reduced 75 per cent or more. Penicillin aerosol alone was effective in slightly more than half of the nonsurgical patients. Of 20 patients treated with combined penicillin and streptomycin aerosol 18 obtained a satisfactory result. Urticaria developed in 3 patients and arthralgia in 2 patients treated with penicillin aerosol. The reactions could be controlled by administration of benadryl. A valuable adjunct to nebulization therapy may be the direct intratracheal administration of penicillin and streptomycin.—*Nebulization Therapy in Bronchiectasis: The Use of Penicillin and Streptomycin*

*Acrosols*, A. M. Olson, J. A. M. A., July 12, 1947, 134: 947.—(H. Abeles)

**Management of "Captive" Lung.**—Decortication is used in military surgery to provide for expansion of a useful lung. This is accomplished by removing the "coat" or "peel" of organizing fibrin. This principle can be applied to civilian surgery. The requirements for pulmonary reëxpansion are: (1) some air must enter the lung, (2) the lung itself must be capable of reëxpansion and (3) the remaining content of the hemithorax must suffer a decrease in volume corresponding to requirement one. The factors concerned are: (1) bronchial obstruction, a) large bronchi, b) small bronchi; (2) pulmonary, a) defects of alveoli, b) defects of interstitial tissue, c) defects of alveoli and interstitial tissue; (3) pleural, a) air—i: simple pneumothorax, ii: bronchopleural fistula, valvular or non-valvular, b) fluid, c) fibrin, d) pleural investments. In evaluating a case, bronchoscopy and clinical study will elucidate factors one and two, while thoracocentesis will determine most features of factor three. In a case where there are no known bronchial and pulmonary factors, and where the lung will not reëxpand with pleural aspiration, a decortication must be done.—*Lung Mobilization: Its Indications in the Management of the "Captive" Lung*, H. T. Langston, Surg., Gynec. & Obst., September, 1947, 85: 501.—(A. G. Cohen)

**Arteriovenous Aneurysm.**—A 27-year-old woman had cyanosis since birth, episodes of syncope and paroxysmal nocturnal dyspnea. Physical examination showed numerous, small, superficial hemangiomas on the face, lips and palms. The hemoglobin was 21.6 g., the red blood cell count was 8.2 million. The roentgenogram of the chest revealed a tumor in the right lower lobe. Following a lobectomy the cyanosis decreased, the hemoglobin dropped to 18.4 g. and the red blood cell count to 6.7 million. The pathological diagnosis was arteriovenous aneurysm measuring 4 cm. in diameter.—*Pulmonary Arteriovenous Aneurysm with Secondary Polycythemia: Report of the First Case Treated by Lobectomy*, W. H. Beier-

walles & F. X. Byron, J. A. M. A., July 26, 1947, 134: 1069.—(H. Abeles)

**Aerosol Penicillin.**—(1) A combined steam generator and aerosolizer is described, which effectively produces aerosols of penicillin whose inhalation is capable of providing good therapeutic levels of this agent in the blood. (2) Penicillin dissolves readily in propylene glycol to form an effective, stable aerosol. The addition of glycerin (5 per cent) further stabilizes the aerosol. (3) Methods of conserving the aerosol for maximum utilization include simple open inhalation; inhalation within an air-tight chamber or transparent portable tent, and inhalation from a breathing box. (4) Unusually high and prolonged levels of penicillin were obtained in the blood when a penicillin-propylene glycol aerosol was inhaled within a tent or from a breathing box. (5) The tent method should be ideal for the treatment of infants and children or whenever continuous treatment with penicillin is indicated. (6) Propylene glycol, by inhalation of its aerosol and by intravenous or intramuscular injection, imparts to the blood serum a pronounced inhibitory action against a strain of *Bacillus subtilis* (an attribute not possessed individually by either the propylene glycol or the serum). (Authors' Summary).—*Aerosol Penicillin: Blood Levels of Penicillin by Inhalation of Aerosols Produced by a Combined Steam Generator and Aerosolizer, With the Use of Propylene Glycol, Tents and a Breathing Box*, S. J. Prigal, T. H. McGavack, F. D. Speer & R. Harris, J. A. M. A., July 12, 1947, 134: 932.—(H. Abeles)

**Bronchial Catheterization in Lung Abscess.**—The treatment of lung abscess with direct penicillin instillation into the abscess cavity is outlined. Among the cases under observation 40 per cent of abscesses were found in the dorsal segment and 13 per cent in the apical segment of the upper lobe, 15 per cent in the right middle lobe, and 13 per cent in the apex of the lower lobe; 75 per cent of abscesses were localized in the right lung. The technique of introducing the catheter into the various pulmonary

segments is described in detail. The dosage of penicillin was 100,000 units in 10 cc. of saline instilled directly into the abscess cavity. In acute severe cases instillations were performed once daily for a period of ten to fifteen days. In milder cases a total number of 6 to 8 instillations were given every other day. If necessary the series was repeated after an interval of one week. The method is said to be without serious accidents. Hemorrhage, without any further consequences, occurred 5 times in 1,500 instillations. No statistical data on results are given.—*La localization radiologique des cavités suppurées intrapulmonaires et leur cathétérisme par voie endobronchique*, C. Mattei, M. Tristani & A. Barbe, *Rev. de la tuberc.*, 1947, 2: 704.—(V. Leites)

**Mediastinal Emphysema.**—Block of the brachial plexus to produce anesthesia of an upper extremity has received increasing use in military surgery. The present series of 700 cases includes many plastic surgery operations, for which brachial block is quite suitable. To inject the plexus the needle is inserted above the middle of the clavicle and aimed downward towards the plexus and towards the apex of the lung. Pneumothorax has been reported as a complication, and even in association with emphysema of the lung and subcutaneous tissues. Five instances of mediastinal emphysema are reported for the first time in the present series. The signs and symptoms of mediastinal emphysema are emphasized by the report of a typical case, in which a pneumothorax developed during the twenty-four hours after the mediastinal changes were noted. None of the 5 patients had any serious respiratory difficulty or complication.—*Mediastinal Emphysema Secondary to Brachial Plexus Block*; E. G. Dimond, B. Root & M. H. Delp, *Bull. U. S. Army M. Dept.*, August, 1947, 7: 718.—(W. H. Oatway, Jr.)

**Ossification of Bovine Lung.**—The first known case of ossified lung in a domestic animal is reported. Ossification of bronchial cartilages and tuberculous or other pulmonary lesions are common in man, but diffuse forms

are rare; only 46 cases had been reported until 1943. There are two varieties of diffuse ossification, the racemose or branching type and the nodular circumscribed type. The racemose is by far the more common, and consists of branching spicules of true bone in the inter-alveolar septa of the lung. They may be the result of a senile metaplasia in the perivascular connective tissue. Marrow-formation is relatively rare in the diffuse forms. The present case report is that of a Texas steer, condemned in a sale-yard because of extreme emaciation. The nodes and other organs were normal, but the lungs were hard and inelastic, especially in the posterior areas. Typical bone-islands ("disseminated" ossification, similar to the racemose type), as well as exudative and proliferative changes, were found in the septa. Some alveoli were atelectatic, while others were emphysematous. Osteocytes were numerous in the bone, but osteoclasts and osteoblasts were absent.—*A Case of Ossification of the Bovine Lung*, W. S. Bailey, *J. Am. Vet. M. A.*, August, 1947, 111: 123.—(W. H. Oatway, Jr.)

**Giant Mediastinal Teratoma.**—This case raised the old, and often difficult problem of the correct diagnosis in a condition characterized only by an increasingly large X-ray shadow in the chest. Throughout the final eight-year course of the disease a number of possible diagnoses were advanced, including pneumonia, hydatid cyst, aneurysm, growth of the thymus, lymphosarcoma, intrathoracic goiter and, finally, because of the mediastinal location and tomographic findings, dermoid cyst. In order to verify this assumption, an exploratory puncture was performed, which yielded a typical brown fluid. A series of punctures furnished some relief but the increasing respiratory difficulty and general exhaustion required surgical treatment. An anterior mediastinotomy was well borne and proved successful in removing over 2,000 cc. of hair, sebaceous matter and cystic fluid. Present condition of the patient is excellent, with gain in weight, normal respiration and ability to sleep.—*Teratoma gigante de mediastino*, M.



*Benzo, Bol. Inst. de pat. méd., Madrid, February, 1946, 1: 23.*—(A. A. Moll)

**First Case of Histoplasmosis in Colombia.**—A case of histoplasmosis is described as a post-mortem finding. The patient was a woman 56 years old, a native of Venezuela, who died in the Cúcuta hospital after a seven-day illness. Typhoid was reported as the cause of death. This is the first case of the disease seen in Colombia and the diagnosis was confirmed both by Colombian and Brazilian experts. Histoplasmosis has been described from various parts of South America since Darling first found it in Panama in 1906. Negroni in Argentina reported the first South American case in 1940.—*Histoplasmosis en Colombia, A. Gast Galvis, Rev. de med. y cir., Colombia, S. A., May, 1947, 14: 12.*—(A. A. Moll)

**Histoplasmosis.**—Two cases have been recorded from Wisconsin to bring the total number of reported cases to 80. It is generally a fatal systemic disease caused by the yeast-like fungus named *Histoplasma capsulatum* which may be found in the reticulo-endothelial system and is probably transmitted from animals, notably dogs. The four principal clinical features of the disease are: (1) gastrointestinal manifestations of ulceration and diarrhea, (2) skin findings of chronic ulcerations and abscess formations, (3) cardiac or joint manifestations, (4) lymphadenopathy, hepatomegaly and splenomegaly. Lung findings are recorded in about 20 per cent of the cases and are not characteristic and frequently are confused with tuberculosis, especially the pulmonary calcifications. The cases of histoplasmosis have usually presented a gross picture similar to that of leukemia. Caseous necrosis of the adrenals is particularly common in these patients. Histologically the organisms are found throughout the reticulo-endothelial system contained in the phagocytic reticulum cells. Secondary anemia, leukopenia and thrombocytopenia have been frequent. It is of interest that the majority of histoplasmin reactors are demonstrated between 5 and 25 years of age; whereas, the tuberculin reactors are found in the third

and fourth decades. In those who are histoplasmin-negative and tuberculin-positive, the incidence of pulmonary calcifications is about 17 per cent; those with histoplasmin-positive and tuberculin-negative skin tests have pulmonary calcifications in slightly more than 90 per cent.—*Histoplasmosis: The Pathological and Clinical Findings, J. F. Kuzma, Dis. of Chest, July-August, 1947, 13: 338.*—(E. A. Rouff)

**Osteochondritis Vertebræ (Calvé).**—Descriptions of this condition are very misleading. The correct definition is *osteochondritis vertebræ* of the primary ossification centres occurring before age 10. It is thus distinguished from *osteocondritis vertebræ* of the secondary ossification centres (epiphyseal plates) often named Scheuermann's disease or juvenile kyphosis. The author speculates that Calvé's disease may be caused by tubercle bacilli of low virulence. A case is reported.—*The Relationship between Tuberculosis and Osteochondritis Vertebræ (Calvé), F. Leeser, Am. J. Roentgenol., June, 1947, 57: 744.*—(J. E. Farber)

**Tuberculosis Control.**—The problem of tuberculosis control in the French army may be considered under three main headings: (1) the discovery and elimination of all tuberculous personnel as soon as possible after induction, (2) maintenance of health of the standing army, and (3) prevention of spread of the disease in the civilian population by discharged tuberculous army personnel. In order to accomplish the first aim, those called to active military duty are required to bring health certificates from their own physicians. These certificates in conjunction with a preliminary examination by a medical board eliminate a certain number of persons who are then sent to a chest centre for clarification. All those passed upon by the first board are brought up before a review board. There they are subjected to an even more detailed examination including systematic radiography of the chest. All abnormal conditions are referred to a special chest centre where they

are classified into the following groups: open tuberculosis, closed tuberculosis, suspected tuberculosis, pleural or pleuro-peritoneal tuberculosis, and "surgical" tuberculosis (including lymph node, genito-urinary, bone and joint, etc.). To achieve the second aim, namely the maintenance of health of the existing army, military physicians are constantly primed on recognition of early signs and symptoms. A continuous fight against predisposing causes, such as they are known, is waged by the army medical personnel. The most effective weapon in this fight is the periodic X-ray reëxamination of all personnel. The number of cases discovered by such means is still considerable, amounting to 0.8 to 0.9 per thousand in a group so examined. In 1946, tuberculin testing of recruits was done, and it was found that nearly 50 per cent were tuberculin-negative. Retesting of the nonreactors will be done in the future as a case-finding measure. Universal vaccination of these troops with BCG is not being planned in spite of the favorable report of the Academy of Medicine. Vaccination will be limited to volunteers. Further measures consist of careful examination of all contacts of recently discovered cases, and case-finding among the patients' families. Diagnosed cases are placed under medical care as soon as possible. Patients may be institutionalized either in civilian institutions by arrangement, or in one of several government hospitals. Facilities are also available for institutional or preventorium care of dependents of personnel, should such become necessary. In order to safeguard the health of the civilian population, part three of the army's program, a very comprehensive medical-social program is available. The individual and family problems of each patient are worked out by the social agencies in such a manner that the patient is satisfied to accept treatment until he can be discharged safely. Considerable benefits are offered in this connection. The comprehensive program as here outlined is in force for almost one million personnel, both male and female. In addition to all enlisted and commissioned

personnel it comprises the women's army corps, children and adolescents in military preparatory schools, officer candidates, all dependents of regular army personnel, and all civilian workers employed by the war department.—*La prophylaxie de la tuberculose dans l'Armée française*, Debenedetti & Dutrey, *Schweiz. med. Wehnschr.*, May 31, 1947, 77: 591.—(H. Marcus)

**Hospitalization Cost.**—Data on the cost of methods for control of tuberculosis in general hospitals have not been available. The need, feasibility and value of control methods are now well known—personnel members should be recurrently examined by a suitable X-ray method; all newly registered patients and outpatients should be screened by radiography for tuberculous disease; and tuberculous patients, whether admitted for therapy or newly-found, should be cared for with adequate isolation technique. Unrecognized disease among new admissions, and the hazard to personnel in contact with patients have been demonstrated. Control procedures are increasing but not wide-spread enough. Accounting methods, disinterest, and a fear of the results have further limited the field from which data can be obtained. For the present survey, information was obtained from hospitals and sanatoria which were known to have experience with control measures; they are of various sizes and types, and are in four different areas of the United States. Cost data were also obtained from the health departments of five states, from several hospital, radiology, and tuberculosis societies, and from the U. S. Public Health Service. All of the data are previously unpublished. The general costs of tuberculosis to society, the state, and to individuals are mentioned. The cost of care of tuberculous patients in sanatoria is presented as a comparison to the cost in general hospitals. The cost and charges for care of tuberculous and nontuberculous patients in hospitals were obtained from twenty administrators of general hospitals. The hospitals included several with a 95- to 200-bed capacity, and several with 500 to

3,400 beds. The figures differ widely, depending on the type of hospital, the services rendered, and the size of the unit. They were mostly derived from experience during the fall and winter of 1946-1947. Analysis of the data shows the surprising fact that *cost and charges for care on tuberculosis units* were usually *the same or less than for care on other services*. In large tuberculosis units the cost was markedly less, and comparable to sanatoria of a similar type. The same services were provided, plus some degree of infectious disease precautions and, frequently, chest surgery. A survey of the expense of isolation technique was made and listed. Many hospitals and sanatoria use only a few essential sanitary procedures. The total cost of precautionary methods could not be estimated, but basic *services* cost little if any more than for care of nontuberculous patients, and basic *materials* cost only a few cents a day per patient. (Whatever the cost, it is already included in the low cost of care.) The cost of constructing facilities for care of tuberculous patients is discussed. New construction is expensive and rarely necessary; the usual need is for small units or rooms, and these may be had by conversion of existing space at a very low cost. The costs of compensation and insurance are discussed—the former is high and rising; the latter has not yet been affected by use of control measures, although the door is open whenever sufficient experience shows a favorable result. The use of subsidies to cover the costs of control measures has been investigated. Many hospitals are now given partial or complete support for case-finding surveys from various sources. Many states now subsidize the care of some (or most) tuberculous patients in order to obtain coöperation, isolation and care. The federal government, through the Veterans Administration and hospital-aids program, has shown the same tendency. The cost of case-finding by X-ray methods is described. A relatively small number of hospitals has a complete survey program, though it is increasing quite rapidly; the most suitable method will depend upon the money or equip-

ment available, and on the case-load. Small hospitals will probably use full-size films on paper X-rays; the cost per patient should range between 50 cents and a dollar, plus possible reading costs. Large hospitals, and those able to afford special equipment, will use miniature films of some sort. None of the hospitals which use small films had data on costs, due to the use of subsidies, but figures were obtained from numerous surveys by the mobile units of state health boards and the U. S. Public Health Service. Such figures were modified by the varying costs which had to be included, and have increased since 1943-1945. The range was from 21 to 69 cents per capita, which can be reduced 30 to 75 per cent in stationary hospital units by the subtraction of travel costs, salaries, publicity, etc., and by the use of existing hospital equipment and personnel. The cost of film-reading is minimized by the help of staff members and the coöperative attitude of the College of Radiologists. The cost of new photoroentgen equipment ranges from \$3,800 to \$5,500 for machines without energizing equipment, to \$9,000 or more for complete units. Most hospitals have absorbed the cost of case-finding, but a few are known to charge a flat-rate fee, the same as for admission blood tests.—*The Economics of Tuberculosis in General Hospitals*, W. H. Oatway, Jr., *Hospitals*, November, 1947, No. 11, 21: 54.—(W. H. Oatway, Jr.)

**Primary Tuberculosis.**—A group of children from tuberculous families giving evidence of latent or manifest primary infection was subjected to periodic follow-ups between the years 1925-1941. The initial group consisted of 378 children up to the age of 4. In this group 236 cases showed only a positive tuberculin reaction, 120 had pulmonary foci and adenopathies and 22 had acute progressive forms (miliary tuberculosis, caseous pneumonia). The total tuberculosis fatality in this age-group was 9.5 per cent (34 cases), two-thirds of which fell into the first year. The next group included 270 children between the ages of 5 and 10 with a tuberculosis

fatality of 3.7 per cent, almost exclusively from tuberculous meningitis. The incidence of pulmonary foci was lower than in the first group. There were 4 cases of benign pulmonary infiltrations and 8 cases of extrapulmonary tuberculosis. In 1940-1941 a group of 218 children between the ages of 11 and 18 underwent the final examination. Among the 118 cases in the age-group 11 to 13, 6 cases had benign lung involvement in form of circumscribed infiltrations or disseminated lesions. One-third of the whole group gave evidence of what is described as chronic "tuberculous intoxication" which is being attributed to persistent activity in the lymph node component of the primary complex. In the age-group 14 to 18 only 64 per cent could be considered as in good health. The others gave evidence of active primary tuberculosis in its protracted form with different clinical manifestations or various forms of pulmonary tuberculosis mostly localized in the upper lung-fields with tendency to progression. Among 52 adolescents in the age group 16 to 18, every fifth showed a relatively fresh pulmonary process, every tenth had a positive sputum. The connection of these grave progressive forms with primary infection acquired in early childhood is considered most probable. In another group of 94 children having been exposed to tuberculosis in childhood, 13.2 per cent developed tuberculosis during adolescence, whereas among 124 children from nontuberculous milieu the incidence of pulmonary tuberculosis during adolescence was only 7.2 per cent. The effect of continued superinfection on latent or active primary tuberculosis could not be definitely established on this material: a group of 38 children infected during early childhood and subjected to prolonged or repeated superinfection until adolescence developed pulmonary tuberculosis in 10.5 per cent of cases. The incidence of pulmonary tuberculosis in a similar group with no possibility of superinfection was 9.5 per cent.—*Early and Remote Effects of Tuberculous Infection Acquired during Early Childhood,*

*B. L. Jachnis, Probl. tuberk., 1947, No. 3, 26.—(V. Leites)*

**Primary and Reinfection Tuberculosis.**—Tuberculin studies both in animals and persons have demonstrated that the body may lose, after a certain period, its ability to react to tuberculin. The finding in adults of modalities affecting both nodes and lungs, and comparable in every way to those seen in primary infection in children, led to the belief that they represented late primary infections. The detection of this type of lesion in patients tuberculized long before and having signs or history of an old tuberculous process shows that caseated nodes should be attributed to constitutional peculiarities unconnected with tuberculin allergy. At present, it is impossible to establish the diagnosis of primary infection in adults, as it cannot be based on the reversion of the test or the verification of an infantile type tuberculosis. Differentiation of primary and reinfection lesions is difficult and, as shown by Israel and Long, has no practical value. On the other hand, recognition of the node involvement becomes significant because the course is frequently more serious in this type. The new genetic studies, supplementing biometric and general data, have demonstrated the hereditary transmission of a greater degree of resistance or susceptibility to tuberculosis in receptive animals and persons. When considering the clinical, epidemiological and social aspects of the disease, the significance of the soil factor cannot be disregarded. The observations made among the Bolivian Indians during the Chaco War and by Marais (1946) among South African natives working in the mines bear out this conception, which has also been emphasized by Monge in Peru. Pathological and X-ray studies by Scandroglio and Rodríguez among people of all ages dying from violent causes in Montevideo showed that at about 22 years of age calcifications are found in 100 per cent of cases, while tuberculin reactor rates at that age do not exceed 80 per cent. In other words, 20 per cent of those people (and the percentage is

even higher at the age of 15) have lost their ability to react to tuberculin.—*La tuberculosis primaria y de reinfección del adulto (su significado clínico, epidemiológico y social)*, F. D. Gómez, *Clin. tisiol (Rio de Janeiro)*, October-December, 1946, 1: 285; and also *Rev. brasil. de tuberc.*, November-December, 1946, 15: 489.—(A. A. Moll)

**Perforating Lymph Nodes.**—In the opinion of Mounier-Kuhn and Dufourt perforation of caseous lymph nodes into the bronchus following active primary tuberculosis is a much more frequent occurrence than hitherto suspected. The authors are here not referring to the well known manifestations of perforation in its massive form, but to its less pronounced aspects. Routine use of bronchoscopy in adults and children with primary infection revealed the frequent presence of very small bronchial fistulae, often difficult to visualize because of secretions or edema of the bronchial wall. These bronchoscopic findings were seen in association with a very characteristic X-ray pattern: there was a more or less circumscribed area of fine, nodular, partly confluent infiltrations extending from the hilum and usually not quite reaching the periphery. Tomography revealed in the region of the infiltration the image of a bronchus with thickened contours, indicating disease of the bronchial wall. Clinically these small perforations remained mostly silent or gave few uncharacteristic symptoms. The prognosis was good. There was spontaneous closure of the bronchial fistulae. The pulmonary infiltrations persisted for three to six months and then showed gradual regression. If the perforation was larger the pulmonary involvement due to bronchial dissemination was more extensive occupying a pulmonary segment or a whole lobe. These cases, without being alarming or rapidly fatal, have a more serious prognosis and pneumothorax should be considered. Fibrotic or calcific changes formed a residue of these pulmonary infiltrations. The X-ray film of a child or adolescent showing a circumscribed area of multiple small calcific

densities, situated mostly in the middle or lower lung-fields, permits according to the authors to make a retrospective diagnosis of curable lymph node perforation into the bronchus during the course of primary tuberculosis. It is stressed that the described pulmonary infiltrations, belonging to the primary and post-primary period, should be strictly differentiated regarding pathogenesis, prognosis and treatment from infiltrations of the reinfection period, such as the early infiltrate or others, which they may resemble roentgenologically.—*Les infiltrats pulmonaires secondaires d'origine ganglionnaire*, A. Dufourt & P. Mounier-Kuhn, *Rev. de la tuberc.*, 1947, 11: 155.—(V. Leites)

**Tracheobronchial Tuberculosis.**—Among 151 patients (73 men and 78 women) in a tuberculosis hospital in Rio de Janeiro bronchoscopic examination revealed in 59 (39 per cent) tracheobronchial lesions. In 40 some type of collapse therapy was tried: 24 pneumothoraces, 12 thoracoplasties, 3 phrenicectomies (with very poor results), and one extrapleural pneumothorax. In a two-year period 7 of these 40 cases (11.8 per cent, as compared to 21.2 per cent in the entire group) died, 13 progressed unfavorably, 5 became arrested and 14 either improved considerably or healed clinically. When tracheobronchial and visceral pleural lesions coexist pleural complications may develop during pneumothorax treatment. Although pleural lesions seem more responsible, there should not be disregarded the possibility that empyema may be due to the spread of the suppurative process caused by the catarrhal retention. All changes in the mucous membranes in the trachea and larger bronchial tubes, including extensive catarrhal infiltration, were listed, tuberculous and secondary bacterial processes being usually associated. In local treatment, even when tuberculous ulceration was present, sulfanomides or penicillin was tried. Pleuroscopic examination should decide whether pneumothorax should be continued in such cases or another method of treatment substituted.—*A traqueo-*



November-December, 1946, 15: 505.—(A. A. Moll)

**Emphysema in Tuberculosis.**—Emphysematous changes in pulmonary tuberculosis may be classified as intrafocal, perifocal, interstitial, diffuse (compensatory), bullae and blebs. The pathogenesis of intrafocal and perifocal emphysema is bronchial and bronchiolar obstruction. The perifocal form is the most common type. Interstitial emphysema is found in artificial and spontaneous pneumothorax. A bleb is formed when the lung is separated from the pleura by interstitial emphysema. In bullae the pleura retains its connection with lung parenchyma. Primary tuberculous foci may be enveloped in microscopic areas of perifocal emphysema. Hematogenous tuberculous foci may show several types of emphysema: intrafocal, bullae and blebs. The chief cause of localized hypertrophic emphysema is bronchial obstruction. The latter is produced by exudate, necrotic material, endobronchial tuberculous lesions, compression, torsion and stretching. Atrophic emphysema is largely due to vascular changes.—*Pulmonary Emphysema and Tuberculosis*, A. Guggenheim, *Am. J. Roentgenol.*, July, 1947, 58: 64.—(J. E. Farber)

**Tuberculostasis by Streptomycin.**—The present study was undertaken for the purpose of clarifying the bacteriostatic vs. the bactericidal effects of streptomycin on *M. phlei*; *M. avium*; *M. tuberculosis* var. *hominis* no. 607, nonpathogenic strain; *M. tuberculosis* var. *hominis* H37Rv, pathogenic strain; *M. tuberculosis* var. *hominis* H37RvR, streptomycin-resistant pathogenic strain. The method of growing the organisms for bacteriostatic tests has been described elsewhere (Smith, 1947). For bactericidal studies, the cultures were plated out on suitable agar media, incubated for varying periods of time at 37°C., and all colonies counted. The results show that streptomycin has not only a bacteriostatic but also a marked bactericidal action upon different strains of *M. tuberculosis*. The size of the inoculum and the time of incubation

are of great importance in determining the bacteriostatic and bactericidal activity of the antibiotic. In a growing culture of tubercle bacilli, there was a decrease rather than an increase in the proportion of streptomycin-resistant cells with an increase in age of the culture. When streptomycin and streptothricin were combined, their effect upon tubercle bacilli was additive rather than synergistic. The principal effects of streptomycin on the morphology of tubercle bacilli were loss of acid-fastness, increase in granulation, and, in highly bacteriostatic concentrations, shortening of the rods.—*Tuberculostatic and Tuberculocidal Properties of Streptomycin*, D. G. Smith & S. A. Waksman, *J. Bact.*, August, 1947, 54: 253.—(F. G. Petrik)

**Streptomycin Resistance.**—To study some of the factors which result in the production of streptomycin-resistant strains of tubercle bacilli, sputa of 8 patients having far advanced pulmonary tuberculosis and being treated with the drug were used in experimental work. Cultures were obtained before institution of treatment and at weekly intervals thereafter for a period of four to five months. All cultures were made on Herrold's glycerine-egg medium. Sensitivity of the bacilli to streptomycin was determined at the first inoculation by adding streptomycin in varying concentrations to the medium and inoculating plates of plain and streptomycin-containing media simultaneously with equal amounts of treated, concentrated specimen of sputum. To determine the potency of streptomycin after it had been added to Herrold's medium, assays were carried out over a period of seven weeks, using a modification of the cup method of Stebbins and Robinson. No appreciable diminution of potency of streptomycin was detected. Patients included in the study received 1 g. per day intramuscularly, in divided doses at six-hour intervals. In 7 of the 8 cases a few relatively resistant organisms were found to be present in cultures before institution of chemotherapy. In 4 of the cases, the original

predominantly sensitive strains of bacilli isolated were replaced during chemotherapy by strains more resistant to the drug. Weekly cultures showed a gradual increase of the number of resistant organisms, beginning one to four weeks after institution of therapy. It was observed that resistant organisms grow comparatively slowly on media containing streptomycin, although the rate of growth tends to increase as greater degrees of resistance appear. Although the mechanism of drug resistance is an unsolved problem, evidence indicates that the factors of genetic variation and selection may be of prime importance.—*Relative Numbers of Resistant Tubercle Bacilli in Sputa of Patients before and during Treatment with Streptomycin*, Marjorie Pyle, *Proc. Staff Meet., Mayo Clin.*, October 15, 1947, 22: 465.—(P. Q. Edwards)

**Streptomycin for Miliary Tuberculosis.**—An infant of 11 months was found to have miliary tuberculosis in September, 1946. Biopsy of a cervical lymph node was positive. One gram of streptomycin per day was given for three months, and was then discontinued because of severe local reactions to the injections. Fever disappeared twenty-four hours after the drug was exhibited; lung signs began to clear in a few days; the lymph nodes were almost normal at five weeks; the miliary lesions in the lungs had cleared by the seventh week of treatment. Normal findings were present at an examination a month after cessation of therapy.—*Streptomycin in the Treatment of Miliary Tuberculosis*, G. Cogley & E. Goettsch, *J. Pediat.*, July, 1947, 31: 70.—(W. H. Oatway, Jr.)

**Streptomycin for Tuberculous Sinuses.**—Eleven Negro patients and one white patient with 60 draining, proven tuberculous, cutaneous sinuses were treated with streptomycin. They received 0.3 g. every four hours, 6 patients for a period of ninety days and 6 patients for a period of 150 days with an interruption of three weeks after the first ninety days. In 9 patients the sinuses developed

from bone lesions, in one following laparotomy and in one it originated in the ischiorectal area. The average length of time the sinuses existed prior to the institution of streptomycin therapy was twenty-four months. Nine sinuses closed within one to four weeks, 9 within six to eight weeks, 30 within ten to twelve weeks and 11 within thirteen to twenty weeks. One sinus is still draining but has shown definite improvement. When a large cold abscess exists in conjunction with tuberculosis of the vertebrae, there is little tendency for the pus to disappear under streptomycin therapy unless it is evacuated by open drainage. Necrotic bone or cartilage should be removed. The average period of observation following closure of the sinuses is four months.—*Streptomycin in the Treatment of Draining Tuberculous Sinuses*, B. L. Brock, J. A. M. A., September 20, 1947, 135: 147.—(H. Abeles)

**Para-aminosalicylic Acid.**—The efficacy of para-aminosalicylic acid in experimental tuberculosis is being investigated by numerous workers at the present time. A recent study of use of the drug in guinea pig infection has yielded pertinent information. Each of a series of adult male guinea pigs was inoculated subcutaneously with 0.001 mg. of human type bacilli, strain H37Rv. Six weeks later all the inoculated animals were noted to be sensitized to tuberculin administered subcutaneously. Starting on the forty-second day after infection, 17 of the animals were treated daily with para-aminosalicylic acid (PAS) by adding 4 per cent by weight of the drug to the feed, about 1.6 g., and 20 animals served as untreated controls. After 161 days of observation (119 days of medication) the surviving animals were killed for necropsy. Severity of disease recorded for each of the untreated controls leaves no doubt of the potential virulence of the infecting organism. In the treated group, the amount of disease varied inversely with the period of treatment—almost no infection was found in the 9 animals treated for the full 119 days. Concentration of the drug was found to be less



than 0.5 mg. per 100 cc. of blood at the time of autopsy. No toxic effects of PAS were observed. Potential effectiveness of PAS in tuberculous infection is indicated by these results, in view of the fact that the disease had been established six weeks prior to the beginning of treatment and in those animals that received the drug for the maximum period of treatment the deterrent effects on the disease were definitely impressive.—*Para-aminosalicylic Acid in Experimental Tuberculosis in Guinea Pigs*, W. H. Feldman, A. G. Karlson & H. C. Hinshaw, *Proc. Staff Meet., Mayo Clin., October 17, 1947*, 22: 473.—(P. Q. Edwards)

**Promin and Diasone.**—The effects of promin and diasone as prepared by the Academy of Medical Science of the U. S. S. R. according to the instructions of Feldman were studied *in vivo* and compared to the effects of the imported American products. The experimental animal for promin was the white mouse. It appeared that the Soviet product was of much lesser toxicity than the American one and could be given in daily doses of 30 to 40 mg., whereas the maximum tolerated dose of the American promin was only 15 mg. daily. With this dosage the American promin was found to be ineffective in inhibiting experimental tuberculosis. Soviet promin was given in the above dosage for twenty days to white mice which had been infected intravenously with a virulent culture of bovine bacilli. A definite inhibitory effect on the development of tuberculous infection was noted in these animals as compared to controls. In analogy to the American experiments, diasone was studied on guinea pigs. The daily oral dose was 300 mg. The duration of treatment was seventy-eight to ninety-six days. The animals had been inoculated with a mixture of equal parts of virulent human and bovine type bacilli. The results of these experiments seem to indicate a high chemotherapeutic activity of diasone towards tubercle bacilli, of the human as well as of the bovine type. The maximum therapeutic effect was achieved if administration of the

drug was started simultaneously with the inoculation of the animal. After prolonged treatment degenerative changes were noted in the liver and the kidneys.—*Chemotherapeutic Activity of Some Sulphones in Experimental Tuberculosis*, U. K. Weisfeiler, *Probl. tuberk.*, 1946, No. 4, 51.—(V. Leites)

**Subtilin.**—The present communication deals with the use of a slightly modified Dubos and Davis medium to demonstrate the antibiotic activity of subtilin against a virulent strain of *M. tuberculosis*. The results show that although subtilin regularly inhibited the growth of the strain of mycobacterium used in concentration of 1:400,000, subsequent animal inoculation revealed that its bactericidal property *in vitro* was low. It required a concentration of 1:20,000 to sterilize the organisms employed in these tests. Unpublished data indicate that subtilin is precipitated in the presence of sodium chloride. Concentrations of subtilin (University of California Lots 8 and 10) greater than 0.1 mg. per cent appear to be precipitated in the blood. Nevertheless, the marked bacteriostatic effect shown here in conjunction with the low toxicity of subtilin are favorable indications for therapeutic trials. A less toxic salt-soluble fraction of subtilin is now available for such trials.—*Use of Modified Dubos Medium for Demonstration of Antibiotic Activity of Subtilin against Mycobacterium tuberculosis*, S. C. Wong, A. S. Hambly, Jr. & H. H. Anderson, *J. Lab. & Clin. Med.*, July, 1947, 32: 887.—(F. G. Petrik)

**Subtilin in Tuberculosis.**—First human experiments with subtilin, conducted in 1944, failed to show any therapeutic merit in the drug discovered by Fontes Magarão. This was probably due to impurities in the product, as previous results *in vitro* and in animals had been encouraging. A new purified extract was made available by Fontes Magarão in 1946 and used in the present clinical study. Eight cases of pulmonary tuberculosis of various types are reported in all of which general improvement, although in varying

degree, followed the use of subtilin. The new preparation may be used orally or intramuscularly and was employed in both ways in this series. The usual oral dosage is 20 drops a day, taken on an empty stomach. No adverse reactions have been noted so far. Subtilin may be tried either alone or to supplement the accepted methods of treatment. Salle and Jane in Los Angeles are also conducting a trial of the drug.—*Nota previa sobre a ação terapêutica da sutilina na tuberculose pulmonar*, A. Renzo, *Rev. méd. munic.*, (Rio de Janeiro), October-December, 1946, 9: 96.—(A. A. Moll)

**Surgery for Pulmonary Tuberculosis.**—Argentine statistics support those abroad showing that among tuberculosis patients operated, in one-third the disease heals, in one-third it is not influenced and in the remaining third it is unfavorably affected. The conception that primary cases heal readily is not borne out by available facts. Tuberculous infection acts as any other infection and the best place to fight it is at the portal of entry, before it attacks and subdues the nodes. In treatment, the most active agents are those acting on the mechanics of respiration, rest in the first place. Better than pneumothorax, phrenic paralysis should be tried in cases where the base or middle lobe are involved. An extrafascial apicolysis, either alone or combined with the former, or a simple "ligamentolysis" will secure the essential collapse and prove effective in a few months under regular X-ray control. Pneumothorax cannot achieve as much. A typical case in an infant with progressive tuberculosis is reported. A ligamentolysis was followed by recovery within six months and complete normality within one year. The most favorable time for trying collapse is before ulceration develops.—*Nueva orientación terapéutica en la tuberculosis pulmonar*, M. Chapo Bortagaray, *Prensa méd. argent.*, May 30, 1947, 34: 990.—(A. A. Moll)

**Bilateral Collapse Therapy.**—A two-year experience with bilateral collapse therapy in the 100-odd-bed Miguel Pereira Hospital in Rio de Janeiro is reviewed. Many patients otherwise considered hopeless thus recovered. Among 890 patients treated with collapse methods, bilateral collapse had to be attempted 92 times because of excavated lesions in both lungs. A combination of pneumothorax with contralateral thoracoplasty was the most common form of bilateral collapse therapy—24 out of 92 cases—pneumothorax being tried first. Continuance of either mono- or bilateral collapse depends on the results of pleuroscopic examination which should be a routine step in every case. Typical cases are reported. For prognostic purposes the vital capacity data secured spirographically seem most significant. Among 745 pleuroscopies and intrapleural pneumonolyses only 16 (2.14 per cent) failed to show adhesions. Out of the 92 bilateral cases, 83 left the hospital with a repeatedly negative sputum. Four most successful cases of bilateral thoracoplasty are presented at length as they suggest the great possibilities of this method in the future.—*A colapsoterapia bilateral no Hospital Miguel Pereira*, R. Fernandes & J. M. Castello Branco, *Clín. tisiol.* (Rio de Janeiro), October-December, 1946, 1: 303.—(A. A. Moll)

**Traumatic Initial Pneumothorax.**—Previous reports have indicated that trauma to the visceral pleura is inevitable in induction of pneumothorax when using a sharp beveled needle. To ascertain if trauma, with induction of a spontaneous pneumothorax of traumatic origin, were also inevitable when using a short beveled, dull needle, a series of 29 cases is reported. A number 19 dull, short beveled pneumothorax needle was used in the anesthetized chest wall to obtain negative pressure readings on the manometer. When such readings were obtained, the needle was promptly withdrawn in 19 cases without injecting air; in 10 cases a small amount of air, averaging 100 cc., was given before withdrawing the needle. In all but 5 cases out of

the 29, a fluctuation in the negative readings was noted, suggesting that a space had already been created between the pleurae by the time the needle was attached to the manometer. The patients were then observed carefully for pain in the neck or shoulder, indicating that a pneumothorax space was being created. In such cases, an X-ray film was taken immediately; otherwise, if there were no complaints of pain, a film was taken in three hours after the procedure had been completed. Fluoroscopy was found to be unsatisfactory to detect small amounts of air in the pleural space; an expiration film was more reliable. A second film in twenty-four hours was taken on all patients. Results of these observations were that in every case a pneumothorax was present, whether or not a small amount of air had been administered. When air had been given, a larger pneumothorax space than anticipated was invariably demonstrable. In almost all cases, the amount of air in the pleural space was seen to increase during the first twenty-four hours, necessitating deflations in some cases in which extreme dyspnea was present. The amount of air present in these cases was seen to vary with the extent of the disease in the underlying lungs rather than with the type of disease. An average of 15 per cent collapse was noted in moderately extensive disease; 41 per cent in extensive involvement. Caseous infiltrations, contralateral pneumothorax and pulmonary fibrosis all seemed to play a rôle to the extent to which they diminished or excluded functioning pulmonary parenchyma. The explanation for this lies in the hypothesis that, in lungs extensively involved, the remaining functioning parenchyma suffers compensatory emphysema. The site selected for induction of pneumothorax is usually overlying these distended healthy areas and the inevitable trauma in such an area to the visceral pleural membrane allows escape of alveolar air more readily than usual since the distended alveoli retract poorly. Another factor may be in the diminished respiratory reserve of extensively involved lungs which requires the constant activity of the healthy areas, thus delaying

closing of the traumatic perforation and thereby leading to progressive increase in the size of the pneumothorax cavity. Because of these findings, the conclusion is drawn that even with the use of a dull short beveled needle, the real initial pneumothorax is a traumatic one, creating a space to which air is then added. Manometric readings which show a fluctuation with the respiratory cycle, which were found to be present in 24 of the 29 cases studied, indicate that an air space is produced without the introduction of air from the outside, thus substantiating the assumption that visceral pleural trauma is inevitable in inducing pneumothorax. Four case histories are given in detail along with X-ray films showing the progression of the pneumothorax space during the first twenty-four hours, even though no air had been given.—*The Rôle of Traumatism in the Induction of Initial Pneumothorax: Further Studies*, I. G. Tchertkoff & I. J. Selikoff, *Quart. Bull. Sea View Hosp.*, January, 1947, 9: 1.—(P. Q. Edwards)

**Phrenicectomy for Hilar Cavities.**—Among 19 patients with cavities in the upper lobe treated with phrenic exeresis, not one showed any appreciable benefit from the operation. In 15 other cases which had cavities apparently in the hilar region according to X-ray appearance but actually located at the apex of the lower lobe or in the middle lobe, only one instance failed to respond to this treatment. Only one patient out of 8 with lesions in other parts of the upper lobe responded to this operation. Accordingly it is recommended that hilar cavities should be localized not only by anterior films but also by lateral and oblique films and by stereoscopic films. It is always possible to determine by sufficient films if the cavity is localized at the apex of the lower or in the middle lobe on the right side. Cavities in the lower lobe or mid-lobe are best treated by primary phrenicectomy as pneumothorax is less effective in these cases. Cavities at the base of the upper lobe are better treated by pneumothorax, since these cases do not respond well to phrenic exeresis.—

*Contribution au traitement des cavernes dites hilaires par la phrénicectomie*, A. C. Chakar & Z. S. Kösioğlu, *Presse méd.*, June 4, 1947, 33: 381.—(E. Bogen)

**Pneumonolysis and Phrenic Paralysis.**—Case report demonstrating the indication, in certain instances, of severing the phrenic nerve during a pneumonolysis. In this patient two large cavities were present, one of which was situated in the lower lobe. Pneumonolysis succeeded in liberating the upper lobe from all adhesions—the lower lobe, however, remained attached to the diaphragm and the posterior chest wall. It was observed through the thoracoscope that the diaphragmatic motions exerted a pull on the lesion in the lower lobe. The phrenic nerve was severed by cauterization through the thoracoscope.—*Sur un nouveau cas de section du nerf phrénique par voie pleuroscopique*, A. Meyer & A. Davy, *Rev. de la tuberc.*, 1947, 11: 220.—(V. Leites)

**Pneumoperitoneum for Pleurisy.**—Exudative pleurisy is always tuberculous unless proved otherwise. According to Hoefer, one case in 4 without pulmonary involvement visible in an X-ray film dies of tuberculosis, usually within a year. Forty per cent of Burril's large series of cases developed open tuberculosis. Hayasi followed the results of exudative pleurisy in 2,321 cases and 46.8 per cent became open cases as did 33.5 per cent of Michetti's more than a thousand cases. It is certainly most necessary to find if possible some way of preventing such a large proportion of patients with pleural effusion from developing progressive pulmonary tuberculosis. P. E. Weil tried prompt aspiration replacing the fluid with air. Wolf also used this measure. The author believes that the initial infection in pleurisy spreads principally by the lymphatic channels and that only collapse therapy can block them. According to the investigations of Spengler, sediment from pleural effusions settles in the costophrenic angles and consists of cells and bacilli. Inflammatory changes as shown by thoracoscopies are always more intense near the base

of the pleural cavity when an effusion is present. As the fluid is absorbed there often remains in the costophrenic angle what appears to be a thickening of the pleura but is really a mass of cellular detritus and tubercle bacilli. The time of the absorption of the pleural fluid is a critical and dangerous period. After the fluid is gone there often remains for an indefinite time a considerable amount of this cellular infectious sediment which is mistaken for pleural thickening or a band of adhesion. According to the author, this sediment plays an important part in post-pleuritic morbid sequelae, for it always provides the bacilli which find their way into the lymphatic channels or the blood vessels. We must be especially on our guard in cases of *primary* infection with effusion. The author does not think that pneumothorax is always the best method of prophylactic collapse but prefers his combination of phrenic nerve section and avulsion (to paralyze the diaphragm) with pneumoperitoneum. He has employed it in a considerable number of cases with satisfactory results. He does not think it necessary to employ it in very mild cases. These he treats with bed-rest and hygienic measures. His treatment of the moderately severe cases seems quite radical.—*Traitement de la pleurésie exsudative dans le but d'éviter des suites éloignées*, G. Maurer, *Rev. belge de la tuberc.*, 1947, 38: 26.—(A. T. Laird)

**Extrapleural Pneumothorax.**—The author proposes the term "extrapleural substitution pneumothorax" for an operation recommended by him under certain conditions, which consists in supplementing or replacing an incomplete or ineffective pneumothorax with an extrapleural pneumothorax. The latter procedure should result in an extrapleural air space, covering all or nearly all of the area of the preceding intrapleural pneumothorax and thus exerting collapsing pressure on the pleural space, its adherent or thickened walls and the underlying lesions and cavities. In certain cases very extensive extrapleural pneumothorax would be necessary to bring this about, extending even from the apex to

the base. He has used such a procedure in about 40 cases and reports some very satisfactory results. He discusses its use in connection with basal as well as apical lesions, and goes into some detail as regards its risks and the alternative methods of treating the various conditions which he considers to be indications for its employment. The complications which frequently follow the induction of much less extensive extrapleural pneumothorax are so serious that many thoracic surgeons would not undertake the very extensive operations illustrated in the fifteen drawings which accompany the text.—*Le pneumothorax extrapleurale de substitution, P. le Foyer & G. Vallade, Le Poumon, May-June, 1947, 3: 11.*—(A. T. Laird)

**Extrapleural Pneumothorax.**—A study based on the observation of 90 cases over a period of two to eight years. A detailed description is given of the operative technique, postoperative management, complications and their treatment. Good results with closure of cavities and negative sputum were obtained in 45 patients (50 per cent). Improvement with full working capacity was achieved in 12 patients (13 per cent). Unfavorable results are in part attributed to hardships during the war, insufficient sanatorium care, premature reexpansion due to evacuation from hospitals, etc. The total fatality of the operated cases was 10 per cent in nine years. Thoracoplasty following extrapleural pneumothorax is considered technically more difficult, but better tolerated by the patients because of fixation of the mediastinum. A correlation is seen between the type of lung involvement and incidence of complications; pleural complications were most frequently found if pulmonary lesions were of the disseminated hematogenous type with particular involvement of the cortical layers of the lung. As further contraindications are considered: peripheral location of cavities, giant cavities, fresh exudative processes, presence of considerable fibrosis,

extrapulmonary tuberculosis.—*Extrapleural Pneumothorax and Oleothorax in the Treatment of Pulmonary Tuberculosis, T. N. Chrushcheva, Probl. tuberk., 1947, No. 1, 26.*—(V. Leites)

**Extrapleural Pneumothorax.**—Lower extrapleural pneumothorax is considered indicated (1) in cavities of the lower lobes after failure of intrapleural pneumothorax and phrenic paralysis, (2) as a complementary procedure in the presence of upper extrapleural pneumothorax or upper thoracoplasty in the presence of progression of the disease towards the lower lobes. The special operative difficulties of lower extrapleural pneumothorax (due to the anatomy of the fascia endothoracica) are described. The maintenance of the extrapleural space demands even more attention than in upper extrapleural pneumothorax because of the greater tendency towards obliteration and the constant presence of fluid. Replacement of air with oil has to be instituted at an early date. Lower extrapleural pneumothorax constitutes a considerable diminution of the breathing capacity and demands preoperatively a careful evaluation of the function of the contralateral lung.—*Concerning the Question of Lower Extrapleural Pneumothorax, D. P. Muchin, Probl. tuberk., 1947, No. 1, 38.*—(V. Leites)

**Extrapleural Pneumothorax.**—Following extrapleural pneumonolysis, the authors place 50 cc. of serum containing 1,000,000 units of penicillin in the space and remove remaining air. Thereafter air is gradually introduced injecting 100 to 150 cc. daily until adequate collapse is obtained. This procedure, carried out on 62 patients, protects against too sudden collapse with extrapleural pneumothorax and prevents many of the complications otherwise observed. Eight figures illustrate this procedure in one case of bilateral extrapleural collapse.—*Pneumothorax extra-pleural et collapsus progressivus, P. Le Foyer, Presse méd., June 4, 1947, 33: 335.*—(E. Bogen)

# INCIPIENCY AND EVOLUTION OF PULMONARY TUBERCULOSIS<sup>1,2</sup>

## I. The Initial Manifestations of the Disease

DAVID REISNER

Incipient pulmonary tuberculosis has been the subject of voluminous studies for many years, and it is still one of the most widely discussed questions. The problems related to the origin, the pathogenetic mechanism and the pathological character of the initial lesion have been a source of much controversy. These fundamentally important questions are not strictly within the scope of this study and a further discussion of these points must therefore be omitted here. From a clinical standpoint, some of the more significant questions concerning incipient tuberculosis are as follows: the mode of onset of the initial lesion, and its clinical and roentgenological manifestations; the means for its early recognition; its potentialities and relationship to manifest clinical disease; its prognosis and therapeutic management.

In former years a great deal of emphasis was placed on so-called early symptoms and on methods of detection of abnormal physical signs, in an effort to discover early pulmonary tuberculosis. Recent experience has shown how little reliance can be placed on symptoms and physical signs as a means for discovery of the tuberculous lesion of limited extent. The general recognition of the basic principle that in the majority of instances such lesions can be revealed only on roentgenological examination has led to intensive case-finding activities, directed towards early discovery of pulmonary tuberculosis by means of routine chest roentgenograms in apparently healthy persons.

And indeed, the results of these activities have indicated that, in the majority of persons in whom tuberculous changes are found through such routine examinations, the pulmonary lesion is of limited extent, and that about 70 per cent of the cases so discovered are classified as minimal, according to accepted standards (1). It must be emphasized, however, that the terms "early" and "minimal" are by no means synonymous and, as Pinner (2) has pointed out, "early and incipient are strictly and exclusively terms of time," while "minimal is a term indicating extent of involvement." Unfortunately, some confusion has arisen with regard to the proper usage of these two terms. As was indicated in a previous study (3), within the classification of minimal tuberculosis are included dissimilar types of lesions, differing widely in regard to the time of their development as well as to their pathological character, which may vary from truly incipient lesions to some that are obviously old and obsolete. On the other hand, there are many instances in which the extent of the lesion, although well advanced at the time of its initial discovery, may represent an early development of the disease in the chronological sense, the degree of involvement observed at a given time depending on the tempo at which progression has taken place.

<sup>1</sup> From the Bureau of Tuberculosis, New York City Department of Health, 125 Worth Street, New York 13, New York.

<sup>2</sup> Presented, in part, before the Medical Section at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 19, 1947.

Thus it is evident that the mere extent of involvement provides no index as to how early or late the process may be. Consideration of the qualitative type of the pulmonary changes, based on certain morphological characteristics of their roentgenological appearance, is often helpful in so far as it may permit, within broad limits, a differentiation between presumably recent and old lesions. However, conclusions reached on the basis of such findings are indirect at best, often misleading and, therefore, of uncertain validity.

The only available direct clinical criterion for determination of the approximate age of a given lesion is the observation of its development by means of serial roentgenographic examinations. Such successive roentgenograms are of the greatest importance in dealing with the question of the incipency of pulmonary tuberculosis, provided that at least one roentgenogram prior to the demonstration of the initial lesion has been obtained. The closer the interval between the examinations, the more accurate, within given limits, the determination of the approximate age of the lesion at the time of its first roentgenographic appearance.

Suitable material for the study of the beginning phases of pulmonary tuberculosis can be obtained if one has an opportunity to carry out routine roentgenographic examinations of apparently healthy persons at periodic intervals. The number of persons developing the disease in the course of observation will depend on the total size of the population included in such a program, its particular composition, and the period of observation. In the general population, the number of persons developing apparently fresh lesions within a certain time limit, say each year, is known to be quite small. It is considerably greater in certain groups that are selected for observation because of special circumstances, such as unusual conditions of exposure to infection or because of some particular susceptibility to the disease.

It is quite apparent that opportunities to study incipient tuberculosis on the basis of a numerically representative and unselected type of material are rather limited, and there are only few reports available which deal specifically with the problem of the incipient lesion. The majority of the studies that have dealt with the problem of the development of pulmonary tuberculosis are based on observations of selected groups, such as nurses and medical students. Their main emphasis has been on the question of first infection tuberculosis, as it occurs in adolescents and in young adults, and on its relationship to manifest clinical disease. The problem of the incipient manifestations of pulmonary tuberculosis as a whole did not receive adequate consideration in those studies, probably because of the fact that the numbers of cases in the individual groups that have been investigated were not large enough to permit a detailed analysis. More extensive studies on the incipient phases and subsequent evolution of pulmonary tuberculosis are available in the German and Scandinavian literature. The monographs of Braeuning (4) and Malmros and Hedvall (5, 6) are of particular value in this regard.<sup>3</sup>

<sup>3</sup> More recent Scandinavian literature on this topic is cited in the October, 1947 issue of the *REVIEW*, page 278.

A favorable opportunity to study incipient tuberculosis in its clinical and roentgenological aspects was provided through the material of the tuberculosis clinics of the New York City Department of Health. In these clinics large numbers of apparently healthy persons are kept under observation with routine periodic chest X-ray examinations, and it was possible therefore to accumulate a representative group of cases in whom roentgenograms taken before and after the appearance of the initial lesion were available. Routine periodic examinations of persons who had been under observation because of a history of contact with a known case of tuberculosis provided the principal source for this study. It should be pointed out that material collected from a contact group may not be quite comparable with an unselected group of cases, such as one might obtain from studying development of tuberculosis in a sample of the general population. The question may, therefore, be raised to what extent data obtained from a study of cases of this type would apply on a more general basis. However, it was felt that, in spite of this important limitation, the available material offered an opportunity to study some of the more significant clinical aspects of incipient pulmonary tuberculosis.<sup>4</sup>

#### NATURE AND COMPOSITION OF MATERIAL

The material consists of 344 cases in which the development of roentgenologically demonstrable lesions of pulmonary tuberculosis could be observed. Only cases in which the appearance of such lesions could be detected through direct follow-up observation have been included. There is no information available as to the exact size of the population from which this material has been obtained, nor as to the occurrence of additional cases of tuberculosis, other than those included in this series. For this reason, the question as to the total incidence of the disease, or what part of it is represented by this group, cannot be considered here.

*Source of material and selection of cases:* As mentioned before, supervision of contacts with routine examinations at periodic intervals furnished the preponderant majority of the cases. In 309 cases, or in 90 per cent, contact history was the sole reason for the original admission to the clinic. About 6 per cent had previously had normal chest roentgenograms as part of a group survey and subsequently developed pulmonary tuberculosis. The remaining small number of cases had had some symptoms when they were first examined, but at that time presented no evidence of a tuberculous lesion.

The distribution according to the reasons for follow-up examination, at the time of the initial diagnosis of pulmonary tuberculosis, was as follows: In 250 cases, or 73 per cent, contact history was the only reason for subsequent examination; 77 patients, or 22 per cent, had some symptoms; in 3 per cent the lesion

<sup>4</sup> This and the following article contain a summary report on the observations, a statistical analysis of the material and a general discussion of the essential data. A more comprehensive and detailed presentation of the material will be the subject of a future publication in monograph form.



was discovered as a result of a subsequent routine survey; and in the remaining few cases no definite reason for follow-up examination could be ascertained.

Inasmuch as the major part of this material was made up of contacts, it was possible to keep the cases under observation with periodic roentgenograms, in most instances at intervals of six months to one year. The total period of observation from the time of the original clinic admission to the first demonstration of the lesion, varied from one month to six years. In about two-thirds of the cases this follow-up period ranged from one month to two years, and in the remaining one-third it extended for more than two years. The number of periodic roentgenograms obtained prior to the demonstration of the initial pulmonary lesion varied from one to nine, although the majority of the cases had only one or two such examinations.

The principal criteria for selection of the cases were as follows: the availability of one or more chest roentgenograms prior to the demonstration of the initial pulmonary lesion, and development of a radiographically recognizable lesion of pulmonary tuberculosis during the course of subsequent observation.

The interval between the last roentgenogram before demonstration of the pulmonary lesion and its initial appearance on the subsequent film, ranged from one to six months in 124 cases, or in 36 per cent; from seven to twelve months in 126 cases, or in 37 per cent; in 66 cases, or in 19 per cent, it was between thirteen and twenty-four months and in the remaining 28 cases, or in 8 per cent, it was longer than two years. Thus, in 250 cases, or in nearly three-fourths of the material, the initial pulmonary lesion was demonstrated within a period of one to twelve months after a normal roentgenogram had been obtained. The median interval for the entire group was eight months.

The presence of one of the following conditions prior to the initial demonstration of the pulmonary lesion did not preclude the acceptance of such cases into this series: a calcified focus in the lung or in the tracheobronchial lymph nodes typical of an old primary complex; pleural effusion without demonstrable parenchymal involvement; the presence of an active primary type of tuberculosis in a young child at the time of original entry with later regression and apparent healing, followed after some years by development of pulmonary tuberculosis of the reinfection type.

The diagnosis of the tuberculous nature of the pulmonary lesion which had developed during the course of observation was based either on positive bacteriological findings or, in the absence of bacteriological evidence, on clinical data and roentgenological findings obtained during the follow-up period which made a diagnosis of tuberculosis reasonably certain.

*Race, sex and age distribution:* There were 253 white persons and 91 persons classified as non-white. Included in the non-white group were 75 Negroes, 13 Puerto Ricans and 3 persons of other non-white racial stock. Two hundred and fifteen patients, or 62 per cent of the total, were females and 129, or 37 per cent were males. The proportion of males and females was approximately the same in the white and non-white group.

The age distribution on first examination is shown in table 1. It will be noted that there was only a small number of persons less than 10 years of age. More than half of the total, 185 persons, were in the age group, 10 to 19 years, and those 25 years of age or over amounted to 87, or about one-fourth of the total.

The age distribution at the time of the initial detection of the pulmonary lesion is given in table 2. While persons less than 15 years of age made up one-fourth of the total at the time of the first observation, the proportion of this group fell to one-tenth at the time of the initial appearance of the lesion. The differences in age distribution at the time of the first examination and at the time of the initial discovery of the pulmonary lesion are explained by the lapse of time

TABLE 1

*Age distribution at time of first examination, by sex, for white and non-white persons*

AGE GROUP IN YEARS	TOTAL		WHITE		NON-WHITE	
	Male	Female	Male	Female	Male	Female
	Number					
Total.....	129	215	94	159	35	56
Under 10.....	6	10	4	8	2	2
10-14 .....	25	46	22	37	3	9
15-19.....	49	65	31	48	18	17
20-24.....	17	39	15	29	2	10
25-29.....	11	23	9	15	2	8
30 and over.....	21	32	13	22	8	10
	Per cent					
Total.....	100.0	100.0	100.0	100.0	100.0	100.0
Under 10.....	4.6	4.7	4.3	5.0	5.7	3.6
10-14.....	19.4	21.4	23.4	23.3	8.6	16.1
15-19.....	38.0	30.2	33.0	30.2	51.4	30.4
20-24.....	13.2	18.1	16.0	18.2	5.7	17.8
25-29.....	8.5	10.7	9.5	9.5	5.7	14.3
30 and over.....	16.3	14.9	13.8	13.8	22.9	17.8

between the two observations. The age distribution at the time of diagnosis is also in line with the general epidemiological pattern of pulmonary tuberculosis in its relation to age.

It is noteworthy that 58 patients, or 17 per cent of the total, were 30 years of age or over at the time of the initial detection of the pulmonary lesion. While the majority of these persons were in the age group 30 to 39 years, there were some cases in the fifth and sixth decades of life and, in a few instances, even in the seventh and eighth decades. It should be pointed out in this connection that the population from which this material has been obtained was heavily weighted by adolescents and young adults under 25 years. It may therefore not be

unreasonable to assume that had there been a more nearly equal distribution of the base population, the proportion of persons showing the initial appearance of tuberculous lesions after the age of 30 might have been considerably greater than indicated by the above figures.

There were no significant differences in regard to age distribution between males and females. There was a greater proportion of persons in the non-white group who were 30 years of age or over at the time of the first demonstration of the pulmonary lesion than in the white group, 22 per cent in the former as against 15 per cent in the latter.

TABLE 2

*Age distribution at time of initial diagnosis of pulmonary tuberculosis, by sex, for white and non-white persons*

AGE GROUP IN YEARS	TOTAL		WHITE		NON-WHITE	
	Male	Female	Male	Female	Male	Female
Number						
Total.....	129	215	94	159	35	56
Under 10.....	0	2	0	1	0	1
10-14.....	9	24	7	18	2	6
15-19.....	59	77	42	61	17	16
20-24.....	27	50	21	36	6	14
25-29.....	11	27	9	20	2	7
30 and over.....	23	35	15	23	8	12
Per cent						
Total.....	100.0	100.0	100.0	100.0	100.0	100.0
Under 10.....	0.0	0.9	0.0	0.6	0.0	1.8
10-14.....	7.0	11.2	7.4	11.3	5.7	10.7
15-19.....	45.7	35.8	44.7	38.4	48.6	28.6
20-24.....	20.9	23.3	22.3	22.6	17.1	25.0
25-29.....	8.6	12.5	9.6	12.6	5.7	12.5
30 and over.....	17.8	16.3	16.0	14.5	22.9	21.4

#### OBSERVATIONS AT THE TIME OF INITIAL DEMONSTRATION OF THE PULMONARY LESION

*Pathogenetic phase:* In dealing with a group of cases in which pulmonary tuberculosis was found to have developed during observation, some consideration has to be given the question as to what extent such cases may possibly represent instances of primary infection. In view of recent experiences indicating a marked decline of first infection during childhood, this question would seem to be particularly justified for clinical material which is composed largely of adolescents and young adults, such as included in this study.

On the basis of the roentgenological findings alone it is apparently not pos-

sible to make a definite distinction between primary and reinfection types of pulmonary tuberculosis in adolescents or young adults. The observations of Israel and Long (7), and others, indicate that recent primary tuberculosis developing in such persons rarely shows the characteristic roentgenological features of a primary complex of the type commonly observed in children. As evidence of a primary infection may be regarded a change from a negative to a positive tuberculin test within a short time, usually not more than a few months, prior to the demonstration of the initial pulmonary lesion in the roentgenogram.

In the material of this study systematic tuberculin testing was not carried out and conclusive information on that point is, therefore, not available on the entire series of cases. In a certain proportion of the cases there was, however, some evidence of tuberculous infection preceding the initial appearance of the pulmonary lesion. In 43 patients, a positive tuberculin test without other clinical or roentgenological evidence of infection was obtained six months or longer before the first demonstration of the pulmonary involvement. In additional 48 cases calcified foci characteristic of old primary tuberculosis were noted in the chest roentgenogram. Twelve patients had had pleural effusion some time during the course of observation, prior to the first appearance of parenchymal involvement, and in 2 others there was evidence of other forms of extrapulmonary tuberculosis. Four children under the age of 10 at the time of their first examination, had shown roentgen findings characteristic of active primary tuberculosis, with subsequent regression of the lesion, which was succeeded by development of chronic pulmonary tuberculosis after an interval of a number of years. Thus, in 109 cases, or in approximately one-third of the series, there was evidence of a tuberculous infection prior to the first demonstration of the pulmonary lesion.

As regards the remainder of the material, it should be borne in mind that, with few exceptions, the persons included in this study had come under observation because of contact with a known case of tuberculosis. Nearly all of these had prolonged and intimate household exposure to sputum-positive cases of pulmonary tuberculosis, often for a number of years prior to the initial appearance of the pulmonary lesion. It may also be pointed out that experience with tuberculin testing of household contacts to cases of open pulmonary tuberculosis has indicated that the majority of the contacts acquire their infection during the early period of exposure. Thus, while direct evidence of a preëxisting infection is not available for about two-thirds of the cases included in this study, it would be a reasonable assumption that in the great majority of the cases the pulmonary involvement was in all probability not a first infection lesion.

There were a few cases in which the development of the pulmonary infiltration was preceded by both a negative tuberculin test and a normal roentgenogram, and which could be interpreted as possible instances of primary infection. There were only 2 adolescents in whom the pulmonary lesion was accompanied by demonstrable involvement of the tracheobronchial lymph nodes, an indication of a probably recent primary tuberculosis. Hematogenous forms of pulmonary tuberculosis were observed in 12 cases. Two of these patients had acute disseminated miliary tuberculosis and in the others the roentgenological appearance and

distribution of the initial lesions were of the type observed in chronic hematogenous forms. In some of these, the involvement of the lungs was preceded by either unilateral or bilateral pleural effusion.

In the majority of the cases the pulmonary lesions presented no characteristic features which would permit a separation into distinct pathogenetic phases or forms of tuberculosis and they are, therefore, considered under the generic term of chronic pulmonary tuberculosis.

*Extent of lesion:* The extent of involvement at the time of the first detection of the lesion was analyzed in relation to the interval from the last normal roentgenogram. Table 3 shows the distribution according to the stage of disease,

TABLE 3

*Stage of disease at time of initial demonstration of pulmonary lesion, by time interval, for white and non-white persons\**

MONTHS FROM LAST NORMAL X-RAY FILM TO INITIAL LESION	TOTAL		MINIMAL		MODERATELY ADVANCED		FAR ADVANCED	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
White								
Total.....	252	100.0	176	69.8	63	25.0	13	5.2
0-12.....	188	100.0	144	76.6	37	19.7	7	3.7
13-24.....	44	100.0	26	59.1	16	36.4	2	4.5
25 and over.....	20	100.0	6	30.0	10	50.0	4	20.0
Non-white								
Total.....	88	100.0	44	50.0	26	29.5	18	20.5
0-12.....	60	100.0	33	55.0	15	25.0	12	20.0
13-24.....	20	100.0	7	35.0	9	45.0	4	20.0
25 and over.....	8	100.0	4	50.0	2	25.0	2	25.0

\* Does not include 2 cases of miliary tuberculosis and 2 cases of active primary tuberculosis.

for white and non-white persons. Chart I presents the percentage distribution by stage of disease for a group of 248 patients in whom the interval from the normal roentgenogram was not longer than twelve months and the average interval less than seven months.

It will be noted from table 3 that, among white persons, the disease was minimal in 70 per cent of the cases, 25 per cent were moderately advanced and 5 per cent far advanced. The percentage of white patients with minimal involvement was considerably greater when the interval was one year or less than when it was more than one year. With an increase in the interval from one to two years and over two years, there is an increase in the proportion of cases with advanced disease, with a corresponding decrease of those with minimal involvement.

This is to be expected since early lesions are less likely to be found when the interval is more than one year. It should also be pointed out that in more than 90 per cent of the cases in which the interval was one year or less the lesion was discovered as a result of routine periodic chest X-ray examinations. This was not true to the same extent for patients with an interval longer than one year, among whom about one-half appeared for subsequent examination because of symptoms.

Among non-white patients only 50 per cent of the cases presented minimal lesions at the time of their initial detection. Even in the group in which the interval from the last normal roentgenogram was not longer than one year, nearly half of the cases showed involvement of either moderately advanced or far advanced extent. For the entire non-white group, the proportion of far advanced lesions at the time of the initial diagnosis was four times greater than in white persons. These observations indicate that the chances for detection of

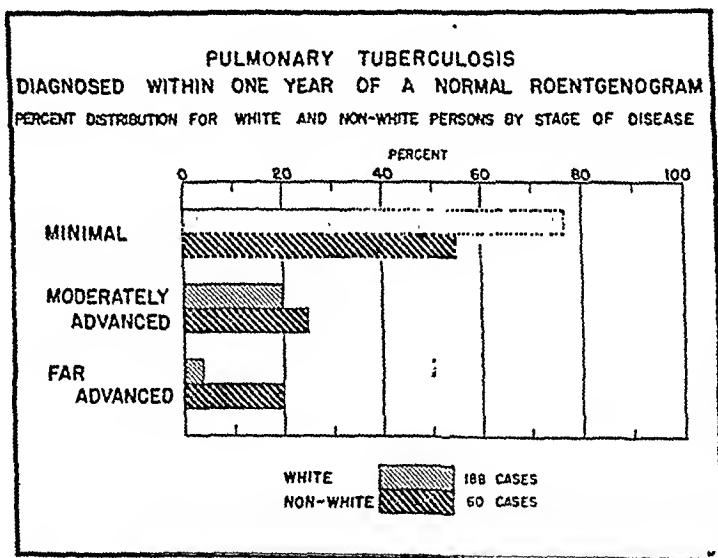


CHART I

early pulmonary tuberculosis of limited extent are considerably better in white than in non-white persons. In the latter, the disease apparently reaches a greater degree of involvement, both more often and within a shorter period of time, than in white persons.

There was no apparent difference between males and females with respect to the extent of the lesion at the time of its initial demonstration. Neither did age seem to be of much significance in this connection, with the exception of non-white adolescents 15 to 19 years of age, among whom about one-third showed far advanced disease at the time of initial diagnosis.

*Location of lesion:* At the time of initial demonstration of the pulmonary lesion, the involvement was limited to one lung in 279 cases, or in about four-fifths of the total, while in 65 cases, or in one-fifth, there was bilateral involvement. There was practically equal participation of the right and the left lung in cases

with unilateral involvement. In 138 patients the lesion was located on the right side, and in 141, on the left.

The overwhelming majority of the cases showed involvement of the upper-lobe area. Purely basal location was extremely rare; there were 15 instances in which the initial lesion was in the parahilar area of the midzone of the lung which usually corresponds to the apical region of the lower lobe. Lesions in this part of the lung have been found to occur more frequently in women than in men and more often on the right than on the left side, an observation which could be confirmed on the basis of this material.

A more detailed analysis of the location of the initial changes in the lung was made in 220 cases in which the pulmonary lesion was classified as of minimal extent, as shown in table 4. In 202 cases, or in 92 per cent, the involvement was unilateral. In 144 cases, or in 66 per cent, the localization was entirely subclavicular. Localization of incipient lesions outside the apical area was about

TABLE 4  
*Location of lesion in 220 cases of minimal tuberculosis*

LOCATION OF LESION	TOTAL		RIGHT LUNG		LEFT LUNG		BILATERAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Total.....	220	100.0	100	100.0	102	100.0	18	100.0
Supraclavicular only.....	42	19.1	21	21.0	18	17.6	3	16.7
Combined supra- and subclavicular.....	34	15.4	7	7.0	16	15.7	11	61.1
Subclavicular: first interspace....	78	35.5	45	45.0	33	32.4	0	0.0
Subclavicular: second interspace....	34	15.4	16	16.0	18	17.6	0	0.0
Subclavicular: first and second interspace.....	14	6.4	2	2.0	8	7.8	4	22.2
Subclavicular: below second interspace.....	18	8.2	9	9.0	9	8.9	0	0.0

three times more frequent than strictly apical involvement, a proportion similar to the one found by Braeuning (4) in a study of 100 cases.

These observations tend to support to some degree the concept of those who, from a roentgenological standpoint, have emphasized the importance of the subapical region of the lung as a site of the initial tuberculous lesion. However, the significance of the apical portion cannot be minimized, inasmuch as in about one-fifth of the cases the lesion first appeared in that area, and in an additional 15 per cent an apical lesion was present along with subclavicular involvement. It must also be borne in mind that the division between apical and subapical localization, on the basis of the roentgenogram, is to some extent arbitrary. The clavicle, which is generally taken as the boundary between these two areas, is by no means fixed in its position and the same lesion may at times appear above and at other times below the clavicle.

Among the subclavicular locations, the pulmonic area projecting into the first anterior intercostal space was the most frequent site with more than half of the

cases. Next in frequency was the second interspace with about one-fourth and in only 18 cases was the lesion located below this area.

*Character of lesion:* Since the roentgenological appearance of the pulmonary changes is extremely variable, it is not an easy matter to attempt a classification which would be relatively simple and at the same time sufficiently descriptive of the types of lesions observed. However, it was felt that a number of fairly characteristic forms occurred with such regularity as to permit a grouping of the initially demonstrated lesions into the following main categories:

- 1: Soft, ill-defined foci, of low density and of flocculent or mottled appearance, usually of small size, one centimeter or less in diameter, less often of larger size, and usually composed of a cluster of smaller coalescent foci.
- 2: Soft, homogeneous infiltrates, usually well circumscribed, either circular or oval, varying in size from about one to 3 cm., but usually larger than the flocculent foci.

TABLE 5

*Character of lesion at time of initial diagnosis in 340 cases of chronic pulmonary tuberculosis by stage of disease*

CHARACTER OF LESION	TOTAL		MINIMAL		MODERATELY ADVANCED		FAR ADVANCED	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Total.....	340	100.0	220	100.0	89	100.0	31	100.0
Soft flocculent infiltrations.....	171	50.3	156	70.9	13	14.6	2	6.4
Circumscribed infiltrates.....	24	7.1	24	10.9	0	0.0	0	0.0
Hard nodular foci.....	24	7.1	19	8.6	5	5.6	0	0.0
Soft infiltrations and hard nodules	37	10.8	21	9.6	16	18.0	0	0.0
Confluent lobular pneumonic type	69	20.3	0	0.0	55	61.8	14	45.2
Massive pneumonic type.....	15	4.4	0	0.0	0	0.0	15	48.4

- 3: Discrete hard nodules, usually multiple, sharply defined and smaller in size than the above two types. A combination with linear or strand-like densities is present in some instances.
- 4: Patchy infiltrations of lobular pneumonic type, sometimes limited to a small area of the lung, but more often consisting of confluent densities of variable extent.
- 5: Massive pneumonic infiltrations involving large pulmonic areas, either of lobar or multilobar distribution.
- 6: Destructive lesions, manifested as areas of cavitation, usually occurring in association with the confluent lobular pneumonic or massive pneumonic type of involvement.

The distribution of the types of lesions observed at the time of initial diagnosis is shown in table 5. It will be noted that, in the material as a whole, there was a decisive preponderance of lesions of the soft infiltrative and pneumonic types, that is, of the group indicated above under 1, 2, 4 and 5, with a combined total of 82 per cent. These forms may be included in the general category of the predominantly exudative type of lesion. Only 7 per cent of the cases were classified as of the discrete nodular and strand-like type, which would correspond with



lesions of an essentially productive character. Mixed forms, such as combinations of the soft infiltrative type of involvement with nodular and strand-like lesions, were found in about 11 per cent of the cases.

This distribution indicates that in the majority of the cases the initial roentgenographic manifestation of pulmonary tuberculosis is a lesion of an infiltrative and pneumonic character, of the type that would suggest a predominantly exudative form of reaction. Findings considered as characteristic of lesions of the productive and fibrotic type were observed only in a small number of cases. There was no apparent correlation between the character of the lesion and the interval from the normal roentgenogram to the first demonstration of pulmonary involvement, though some such relationship might be expected. It should be pointed out, however, that in the majority of cases this interval ranged from a few months to one year. The number of cases in which the interval was longer than one year was not large enough to permit a more extended analysis as to a possible relationship between the time factor and the type of lesions.

The character of the initially observed lesion is of particular interest in those cases in which the involvement was limited to a small area of the lung. This group consisted of 220 cases in which the lesion was classified as of minimal extent. The soft, flocculent, ill-defined type of lesion was the one most commonly observed and was found in 156 cases, or in 71 per cent. Homogeneous, generally well-circumscribed, infiltrates were observed in about 11 per cent, the hard discrete nodular form in 8 per cent, and the remainder of the cases showed combinations of these basic types of lesions.

In the majority of cases with minimal lesions presenting foci of the soft flocculent type, the involvement was well localized and of small size. In nearly half of the cases in which the size of the lesion could be measured, it was one centimeter or less; in one-fourth it ranged from one to 2 cm. and in one-fourth from 2 to 3 cm. In many cases the earliest roentgenological manifestations of the incipient lesion may be quite insignificant and may appear as a localized accentuation of the pulmonary markings, the deviation from the normal pattern being rather questionable. The change from the normal to the pathological state is often gradual, and only by comparison with the preceding roentgenogram will it become evident in such instances. The circumscribed infiltrates are usually of larger size than the flocculent lesions, the majority ranging from 2 to 3 cm. At the time of their first detection, nearly all of them appear as single foci. The hard discrete nodular form consists usually of multiple densities of smaller size than the other two types and they are often scattered.

From these findings it may be concluded that the usual roentgenological manifestation of the initial lesion of pulmonary tuberculosis of minimal extent is a localized infiltration of soft flocculent density. The larger, more conspicuous, homogeneous and circumscribed infiltrates were found to constitute only a small proportion of the initial lesions.

Cases in which the disease at the time of its first detection is found to have reached an advanced stage are, of course, less informative as regards the determination of the point of origin, the character and size of the initial lesion, than

are cases in which the involvement is of limited extent. Nevertheless, such cases are of considerable interest insofar as they furnish valuable information concerning the tempo of the development of the disease.

About two-thirds of the cases in which the pulmonary involvement at the time of initial diagnosis was moderately advanced presented lesions of a confluent lobular pneumonic type. The remainder showed lesions of either the soft flocculent character, the discrete nodular type, or combined forms, but of more wide-spread distribution than the minimal cases. All but 2 far advanced lesions were of the massive pneumonic or extensive confluent lobular pneumonic type.

Wide-spread pneumonic forms were about four times more frequent in non-white than in white patients. This difference was particularly striking in massive lobar or multilobar involvement. In 188 white patients with an interval of one to twelve months from the last normal roentgenogram, there was only one case, or about 0.5 per cent, with this type of lesion. In the 60 non-white persons, 7 cases, or 11 per cent, presented massive pneumonic forms. In the non-white group, massive pneumonic involvement was found to have developed in some cases within a period of a few weeks to three months after a normal chest roentgenogram had been obtained.

At the time of the initial demonstration of the pulmonary lesion, 59 cases, or 17 per cent of the total series, showed definite evidence of cavity. Among 248 cases in which the interval from the previous normal roentgenogram was one year or less, 37 patients, or 15 per cent, had definite cavities when the lesion was first detected. The proportion of cases with initially demonstrable cavity was essentially the same when the maximum interval from the normal roentgenogram amounted only to six months. In non-white persons cavitary lesions were observed about twice as often as in white patients. The greater tendency to destructive forms of pulmonary tuberculosis found in non-white persons is in line with the previously mentioned observations, indicating a decidedly more frequent occurrence of acute pneumonic forms and more rapid progression of the disease in this group.

*Symptoms:* At the time of initial demonstration of the pulmonary lesion only about one-third of the patients complained of some symptoms. The frequent absence of symptoms is not surprising in view of the fact that in the majority of the cases the lesion was detected as a result of routine periodic chest X-ray examination. This was especially true for those cases in which the involvement was minimal. In this group only 18 per cent of the patients had some symptoms, either of general constitutional or local character. Among those with moderately advanced disease, symptoms were present in 54 per cent and, in the far advanced group, all patients had definite symptoms at the time of first diagnosis.

The large proportion of asymptomatic cases, especially in the minimal group, is at variance with recent observations of Abeles and Pinner (8) and Bobrowitz and Dwork (9), who reported the presence of some symptoms in the majority of their cases of minimal tuberculosis. It should be pointed out, however, that the observations of these authors were based entirely on data obtained from a group of sanatorium patients, which cannot be compared with the type of clinical

material in this study. The sanatorium type of case does not represent a random sample of persons with minimal pulmonary tuberculosis, and it is very likely that many of them are being selected for institutional treatment because of some symptoms indicative of activity of the disease. At the same time, it is quite conceivable that under more suitable circumstances, such as those provided by the sanatorium, symptoms may be elicited more often than when the patients are observed in ambulatory clinics.

A consideration of the physical examination is omitted here. In the majority of cases with limited pulmonary involvement, with which this study is primarily concerned, abnormal findings are rarely present. The physical signs that one finds in cases with well advanced disease, although by no means in all, are too well known to need discussion.

*Laboratory findings:* The bacteriological findings considered here include the results of examinations obtained during the first six months after the initial demonstration of the pulmonary lesion, provided that no obvious progression occurred during this period. In cases with definite progression, according to roentgenograms, within the first six months, only the findings obtained prior to the change in the status of the lesion were considered.

Reports of examinations for tubercle bacilli during this period of observation were available in 238 cases, or in about 70 per cent. Positive findings were obtained in 95 cases, or in 40 per cent of those patients in whom at least one examination had been performed. If the cases are considered according to the stage of the disease, the following proportions of positive results are noted: in the minimal group, 20 per cent; in moderately advanced disease, 60 per cent; and in the far advanced group, 90 per cent.

The bacteriological examinations during this limited period of observation were not uniformly adequate according to present standards. Cultures of sputa and gastric washings were employed only in a limited number of cases. A considerable proportion of the cases first came under observation a number of years ago, before the introduction of the more refined methods for demonstration of tubercle bacilli. Also, the practical limitations imposed by the organization of ambulatory clinics, as well as the not infrequent lack of coöperation by the patient, must be taken into account. The proportion of positive findings in patients with minimal involvement was much lower than reported by a number of observers in recent years. It is likely that with more intensive and systematic bacteriological examinations a considerably larger number of positive results could have been obtained.

Other laboratory examinations, such as sedimentation rate, total white blood cell and differential count, were available only in a small number of cases during the initial observation period. Because of the limited information, a further discussion of these findings is omitted.

#### DISCUSSION

In dealing with incipient pulmonary tuberculosis, the question may be raised whether the initial lesion demonstrated by roentgenography actually represents

the first manifestation of the disease. It is quite possible, as has been asserted by some pathologists, that in a number of cases those lesions are preceded by minor pathological changes in the lung which escape roentgenological visualization. However important such observations may be from a pathological or pathogenetic viewpoint, they do not alter the fact that, from a clinical standpoint, the initial lesion demonstrated in the roentgenogram constitutes the first recognizable manifestation of the disease.

Of greater practical concern is the question as to how early in its development can the initial lesion be detected roentgenologically. It is obvious that, even under optimum technical conditions, the lesion must be of a certain minimum size and in a suitable location in order to be visible, as an abnormal density, in the roentgenogram. What the exact limits of visualization are, cannot be accurately stated, but on the basis of experience with this material it would seem that a lesion less than half a centimeter in size is not likely to be clearly visible in the film. It was previously mentioned that not infrequently one may observe a gradual transition from the normal to the pathological state, and that for some time the change may be of such equivocal character as to render a definite interpretation most difficult. The subsequent evolution of such seemingly insignificant changes is often so unpredictable that, unless follow-up examinations are carried out at frequent intervals, the decisive moment for detection of the early lesion of limited extent may easily be missed.

It would, of course, be most desirable to discover the incipient tuberculous lesion when it is still of limited extent and before it has progressed to manifest clinical disease. Is it possible to achieve this result in all, or at least in the majority of the cases? This would depend on two main factors, namely, the time interval at which routine roentgenograms are taken and on the tempo of evolution of the established lesion. It is conceivable that one might come close to the desired goal if it were possible to carry out periodic examinations of apparently well persons at intervals of several weeks to very few months. It is evident that under ordinary circumstances it is hardly feasible to carry through such a plan on a large scale. Usually the intervals between examinations are six months to a year or even longer. The frequency with which the lesion may be detected in its truly beginning phase thus becomes essentially a matter of the tempo at which progression takes place. In the material of this study it was observed that with an interval from the normal roentgenogram ranging from one to twelve months, and an average interval of only a little more than six months, about 70 per cent of the cases presented minimal lesions. In 30 per cent of the cases the disease had progressed during that comparatively brief period to either a moderately advanced or far advanced stage, and in 15 per cent of the group it had gone on to destruction with cavity formation.

In the light of these experiences the question may be asked whether manifest pulmonary tuberculosis usually begins as a small asymptomatic lesion, or whether extensive involvement may be present from the outset. The present findings indicate that a localized lesion of limited extent is the usual incipient manifestation of the disease in the majority of white persons. An acute onset with rapid extension of the disease seems to be the exception in white persons. In

the non-white group, which in this material consisted largely of Negroes, the acute explosive onset was a fairly frequent occurrence. In these cases lesions of a massive pneumonic type were found to have developed within a comparatively short period of time. Within comparable intervals from the normal roentgenogram, the process reached the destructive phase with cavity formation twice as often in non-white as in white patients. In only about half of the cases among non-white persons could an incipient minimal lesion be detected.

These observations seem to indicate that in a large proportion of non-white persons the typical small lesion of incipient pulmonary tuberculosis is either of brief duration and is followed by rapid extension of the disease, or, as it appears quite likely, this initial phase may be entirely non-existent. Not infrequently the disease seems to begin in an abrupt fashion and reaches extensive proportions within a short time after its onset. While such forms are by no means characteristic for the colored group, they occur far more frequently in non-white than in white persons.

The differences in the behavior of the tuberculous lesion as between white and non-white persons will be discussed more fully in the following paper in connection with the observations on the subsequent course and evolution of incipient pulmonary tuberculosis.

The roentgenological findings indicate that the majority of early lesions of limited extent are quite small and of a rather inconspicuous appearance. In fact, as was mentioned before, in the beginning many of them may be on the borderline of the normal. This point is particularly emphasized here because of the great attention that has centered for some years around the "infraclavicular infiltrate" and the "early infiltrate," or the so-called Assmann focus. These forms have been referred to as the classical representatives of incipient pulmonary tuberculosis. The present experience indicates that lesions of these types represent, in all probability, a later and somewhat more advanced phase of the disease than most of the early lesions of limited extent observed in this material. In this respect the present findings are in close agreement with the more recent observations of Malmros and Hedvall (5) concerning the roentgenological manifestations of early pulmonary tuberculosis.

As to the pathological character of the incipient lesions, the roentgenographic appearance suggests that the great majority of them are of a predominantly exudative, pneumonic type. Although the extent of involvement at the time of initial detection of the lesion varies greatly, in most cases in which it is of limited extent it appears to occupy an area which would correspond to a pulmonary lobule or a part of it. While the roentgenographic appearance of the lesion gives no indication as to the presence or absence of caseation, its subsequent evolution strongly suggests that caseous necrosis is probably a very frequent feature of the early infiltration. This interpretation of the roentgenological character of the incipient lesion is essentially in agreement with the observations of Amberson (10).

Since, for understandable reasons, postmortem studies on truly incipient lesions of small extent are not available, it is not possible to adduce definite proof as to the correctness of the above interpretation of their pathological character. At

present, one must rely almost entirely on the roentgenological appearance and on the subsequent behavior of the lesion, a procedure which admittedly is subject to many inaccuracies. In this connection it may be mentioned that in dealing with early lesions one is not always on solid ground in attempting to distinguish changes of an exudative character from those of a presumably productive type. This is especially true for cases in which the earliest manifestation of the disease gives the appearance of small discrete "hard" nodules and which in their pathological substratum are probably not essentially different from the early infiltrations of the "soft," presumably exudative, character.

The location of incipient pulmonary tuberculosis has been the subject of a major controversy between pathologists and clinicians. On the basis of roentgenological findings, most clinical observers have come to accept the so-called subapical location as the typical site of the initial lesion. The present findings confirm the view that in the majority of the cases the initial radiographic manifestation of the lesion is situated in the subclavicular area. It seems, however, that the exclusive importance of this region of the lung, as opposed to the apical area, has been somewhat overemphasized. The observations in this material have shown that in an appreciable proportion of the cases the incipient changes are located entirely in the supraclavicular portion and there is no evidence to indicate that lesions in this location are less important than the subclavicular foci, as far as their potentialities for progression are concerned. It may also be pointed out that, from the standpoint of radiographic technique, the true apical area is probably a less favorable site for visualization of a very small lesion than is the subclavicular portion. It is quite possible that in some cases the initial changes may not become clearly visible until subclavicular extension of an apical lesion has taken place.

Is there a relationship between the age of the individual and his chances of developing pulmonary tuberculosis, after he has previously been found free of any demonstrable lesion? There is a rather wide-spread view that this is much more likely to occur in adolescents and in young adults than in persons above the age of 30 or 35. It is true that the great majority of persons in whom the development of initial lesions has been observed were in the younger age groups. It should be pointed out, however, that the population-groups, which up to now have been studied from this point of view, consisted largely of persons up to the age of about 25. There is, thus far, little information available on sections of the population in which the various age groups were more adequately represented.

In the present material about one-sixth of the cases developing initial lesions during observation were persons past the age of 30. As was pointed out before, there is reason to believe that with a less selected base population, as to age distribution, the percentage of persons beyond the age of 30 may have been larger. Whether the fact that most of the cases had had a history of contact has operated as a selective factor in this particular group, is impossible to affirm or to deny. In a survey of apparently healthy persons in which all age-groups were represented, Robins (11) found that the average age of 25 persons, who had previously had a normal chest roentgenogram and subsequently developed pulmonary tuberculosis, was 33 years.



2



4



FIGS. 1-4

More extensive data, based on studies of large and unselected sections of the population, are needed to provide a definite answer to the question as to the



FIGS. 5-6

relation between age and development of tuberculosis. Although conclusive information on this point is lacking, there is a possibility that a shift towards the

#### ILLUSTRATIVE EXAMPLES

Roentgenograms illustrating types of lesions described in text.

FIG. 1. Small, soft flocculent density in first left anterior interspace. Roentgenogram one year earlier was normal.

FIG. 2. Area of infiltration in left parahilar region, consisting of several smaller confluent flocculent densities. Eight months earlier the roentgenogram was normal.

FIG. 3. Circumscribed "infiltrate" in first left anterior interspace. Normal roentgenogram one year earlier.

FIG. 4. Scattered discrete small nodules in left apex. Roentgenogram was normal six months earlier.

FIG. 5. Confluent patchy pneumonic infiltration on left, showing sharply defined inferior border (sides are reversed in the reproduction). Sputum was positive for tubercle bacilli. Five weeks earlier the roentgenogram was normal.

FIG. 6. Massive pneumonic consolidation of upper lobe of right lung; scattered soft focal areas of infiltration extending to the base. Sputum was positive for tubercle bacilli. A roentgenogram six months earlier was normal. Fatal outcome within five months after first demonstration of lesion.



older age groups may be taking place. The thought suggests itself that the postponement of the first infection from childhood to adult life, which we are witnessing at present, may have a corresponding effect on the age at which the initial manifestation of chronic pulmonary tuberculosis is likely to develop. At any rate, from a practical standpoint, it seems inadvisable to regard the risk of developing the disease as limited to any particular age in adult life.

With expansion of tuberculosis case-finding it may be expected that group surveys will include, in addition to the initial chest roentgenogram, routine examinations at periodic intervals. In order to detect the largest percentage of cases in the incipient stage of the disease, an appropriate interval between examinations would have to be chosen. It is obvious that it would be necessary to strike a proper balance between the desired ideal and what may be considered practicable. The present experience indicates that the optimum interval would be a period not longer than six months between examinations. At yearly intervals the majority of the cases are also likely to be discovered in the minimal stage. A significant percentage of lesions of limited extent will be missed, even with intervals less than one year, but the proportion of cases with advanced disease is bound to be appreciably greater when the intervals are extended beyond the one year period.

The non-white population, particularly Negroes, presents a special problem because of the pronounced tendency of the disease to pursue a more rapidly progressive course than in white persons. This behavior of the disease in the non-white group constitutes a distinct limitation, as far as the chances for detection of the early lesion in the minimal stage are concerned. Nevertheless, periodic examinations at shorter intervals than those regarded as adequate for white persons would seem to be indicated for the non-white population groups.

#### SUMMARY

1. The incipient manifestations of pulmonary tuberculosis were studied in a group of cases in which roentgenologically demonstrable lesions had developed during the course of observation. The material consists of 344 cases, of which 340 presented lesions of chronic pulmonary tuberculosis. The majority of the patients, 90 per cent of the total, were 15 years of age or older at the time of initial detection of the lesion.

2. The great majority of the persons included in this series were contacts who had been under observation with routine chest X-ray examinations at periodic intervals. In 248 cases the initial lesion was demonstrated within a period ranging from one to twelve months after a previous normal roentgenogram and in the remainder, about one-fourth of the total, the interval was longer than one year.

3. Among white persons in whom the interval between the normal roentgenogram and one showing the lesion was one year or less, three-fourths showed minimal lesions at the time of their initial detection, and in the remaining patients the disease had progressed to a moderately advanced or far advanced stage during that period. In the non-white group, which was made up largely of Negroes, minimal lesions were found in only about half of the cases. The pro-

portion of cases with far advanced disease was five times as great in non-white as in white persons.

4. These observations indicate that in white persons pulmonary tuberculosis usually begins as a small localized lesion. This incipient phase is observed less frequently in non-white persons in whom the disease often begins in an abrupt fashion and reaches extensive proportions within a short time after its onset.

5. The roentgenological findings suggest that the early manifestation of pulmonary tuberculosis is usually a lesion of a predominantly exudative, pneumonic character. It may vary in extent from a small localized focus to massive pneumonic involvement in some extreme cases. Lesions of a massive pneumonic type were observed much more often in non-white than in white patients.

6. The usual roentgenological manifestation of the early tuberculous lesion of limited extent is a localized small area of "soft" infiltration, ill-defined and of flocculent appearance. The more conspicuous, circumscribed "infiltrates" were observed only in a small proportion of the cases.

7. In about 90 per cent of the cases the initial lesion was located in the so-called "vulnerable zone" of either the right or the left lung, an area comprising approximately the upper one-third of the pulmonic field. While the subclavicular region was the more common site, in an appreciable proportion of the cases the first demonstrable lesion appeared in the supraclavicular area.

8. The present observations confirm the almost general experience that the great majority of patients with early minimal pulmonary tuberculosis have no symptoms. At present, the only method available for detection of the truly incipient tuberculous lesion is routine chest X-ray examination at periodic intervals.

#### SUMARIO

##### *Incipencia y Evolución de la Tuberculosis Pulmonar. I. Manifestaciones Iniciales de la Enfermedad*

1. En un grupo de casos en el que se habían presentado durante el período de observación lesiones roentgenológicamente demostrables, se estudiaron las manifestaciones incipientes de la tuberculosis pulmonar. El material consta de 344 casos, 340 de los cuales mostraban lesiones de tuberculosis pulmonar crónica. La mayoría de los enfermos, 90 por ciento del total, tenían 15 años o más en la fecha del descubrimiento de la lesión.

2. La inmensa mayoría de las personas comprendidas en la serie consistían en contactos que habían estado en observación con exámenes roentgenológicos periódicos del tórax. En 248 casos la lesión inicial fué descubierta en un término que varió de uno a doce meses después de haberse obtenido una radiografía normal, y en el resto, aproximadamente la cuarta parte del total, el intervalo excedió de un año.

3. En las personas blancas en quienes el intervalo entre el roentgenograma normal y el patológico fué de un año o menos, en tres cuartas partes las lesiones eran mínimas al descubrirlas, y en el resto la dolencia había evolucionado a una etapa moderadamente o muy avanzada durante dicho período. En el grupo no blanco, que estaba constituido en gran parte por negros, se descubrieron lesiones mínimas sólo aproximadamente en la mitad de los casos. La proporción de

casos muy avanzados representó el quíntuplo en las personas no blancas que en las blancas.

4. Estas observaciones indican que en los blancos la tuberculosis pulmonar suele comenzar en forma de una pequeña lesión localizada. Esta fase incipiente se observa menos frecuentemente en las personas no blancas en las que la enfermedad parece a menudo empezar bruscamente y alcanza grandes proporciones poco después de su iniciación.

5. Los hallazgos roentgenológicos indican que la manifestación incipiente de la tuberculosis pulmonar suele consistir en una lesión neumónica de predominio exudativo. En algunos casos extremos puede variar en tamaño de un pequeño foco localizado a invasión neumónica masiva. Las lesiones de este último género fueron observadas mucho más a menudo en los no blancos que en los blancos.

6. La habitual manifestación radiológica de la lesión tuberculosa temprana de tamaño limitado consiste en una zonilla localizada de infiltración "blanda," mal definida y de aspecto floculento. Los "infiltrados" circunscritos más notables sólo se observaron en una pequeña proporción de los casos.

7. Aproximadamente en 90 por ciento de los casos la lesión inicial radicaba en la llamada "zona vulnerable" de pulmón ya derecho o izquierdo, que comprende aproximadamente el tercio superior del campo pulmonar. Aunque la región subclavicular constituyó el asiento más habitual, en una proporción apreciable de los casos la primera lesión fué descubierta en la zona supraclavicular.

8. Las observaciones actuales confirman la observación casi general de que la gran mayoría de los enfermos con tuberculosis pulmonar incipiente de tipo mínimo, no muestran síntomas subjetivos. Hoy día, el único método disponible para el descubrimiento de la lesión tuberculosa verdaderamente incipiente es el examen radiológico del tórax, repetido periódicamente.

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# INCIPIENCY AND EVOLUTION OF PULMONARY TUBERCULOSIS<sup>1,2</sup>

## II. The Behavior of the Initial Lesion and Course of the Disease during Observation Period

DAVID REISNER

In a previous paper (1) dealing with incipient pulmonary tuberculosis, the initial manifestations of the disease have been discussed. The data presented were based on a study of 344 cases in which roentgenologically demonstrable tuberculous lesions had developed during the course of observation. Of these, 340 patients presented lesions of chronic pulmonary tuberculosis. The majority of the cases included in the study were originally contacts who had been under observation with routine chest X-ray examinations at periodic intervals. In this part, the observations on the subsequent behavior of the incipient lesion and the course of the disease during the follow-up period are presented. The paper contains a statistical analysis of the material and a discussion of the essential clinical data. A more complete report on the clinical and roentgenological findings will be published at a later date.

### BEHAVIOR OF THE LESION DURING THE PERIOD OF OBSERVATION

*Length of observation and classification of the behavior of the lesion:* Data pertaining to the follow-up period were obtained either through observation of the patients in the clinics of the Department of Health, from information provided by a number of hospitals and sanatoria or by private physicians. Roentgenograms were obtained for evaluation of the behavior of the lesion during the follow-up period.

The length of observation varied from a period of several weeks or months, in a small number of cases in whom no further follow-up could be obtained, to ten years. Fifty-seven patients, or 17 per cent, were observed less than one year and, of these, 19 died during the first year of observation. In 14 per cent the observation period was from one to two years; in 29 per cent, from two to four years; in 25 per cent, from four to six years; and the remaining 15 per cent were observed up to ten years. The average observation period for the entire group amounted to three years and a half. For the most part, the analysis of the material will be limited to cases in which the period of observation was at least one year, excepting those patients who died during the first year after the initial diagnosis.

The behavior of the lesion was determined by serial roentgenographic observations and was classified into four main categories, in accordance with the following definitions:

- 1: Frank progression: Definite increase in extent of the pulmonary involvement into a more advanced stage of the disease, with or without demonstrable cavitation.

<sup>1</sup> From the Bureau of Tuberculosis, New York City Department of Health, 125 Worth Street, New York 13, New York.

<sup>2</sup> Presented, in part, before the Medical Section at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 19, 1947.

- 2: Slight progression: Evidence of some increase in extent of the lesion, but not beyond the limits of the stage of the disease found at the time of the first diagnosis.
- 3: Regression: Roentgenographic changes indicative of healing of the lesion. This may take place either by complete or partial resolution, by organization or "hardening" with fibrosis, by calcification, or by combination of more than one of these modes of healing. Stabilization of the residual pulmonary changes and the period of observed stability subsequent to regression were regarded as important criteria for determination of the status of disease.
- 4: Stability: No change in extent or character of the lesion noted at any time during the period of observation.

TABLE 1

*Behavior of pulmonary lesion during observation by stage of disease on initial diagnosis for white and non-white persons*

BEHAVIOR OF LESION	TOTAL		MINIMAL		MODERATELY ADVANCED		FAR ADVANCED	
	White	Non-white	White	Non-white	White	Non-white	White	Non-white
Number								
Total*.....	206	78	151	39	46	22	9	17
Frank progression†.....	105	57	75	28	22	12	8	17
Slight progression.....	50	5	38	5	11	0	1	0
Regression.....	47	16	34	6	13	10	0	0
Stability throughout.....	4	0	4	0	0	0	0	0
Per cent								
Total.....	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Frank progression.....	51.0	73.1	49.7	71.8	47.8	54.5	88.9	100.0
Slight progression.....	24.3	6.4	25.2	12.8	23.9	0.0	11.1	0.0
Regression.....	22.8	20.5	22.5	15.4	28.3	45.5	0.0	0.0
Stability throughout.....	1.9	0.0	2.6	0.0	0.0	0.0	0.0	0.0

\* Does not include 2 cases of military tuberculosis, 2 cases of active primary tuberculosis, 38 living patients observed less than one year and 18 patients with pneumothorax treatment within a short time after initial diagnosis.

† Includes 10 patients who received pneumothorax treatment within a short time after initial diagnosis, but showed frank progression during observation.

A distinction between cases showing frank progression and those showing only slight progression, according to the above criteria, was thought justified from a clinical point of view. It was felt that the generic term "progression," without further qualification, was too broad and that it failed to provide an adequate index for determination of the extent to which the lesion had progressed.

*Progression:* Table 1 shows the behavior of the lesion during the period of observation, according to the stage of the disease at the time of the initial diagnosis, for white and non-white persons. In this and in the subsequent tables the data for males and females were combined, since analyses showed no significant

differences between the sexes with regard to the behavior of the disease. It will be noted that, among those cases in which the lesion was detected in the minimal stage, nearly half of white and 72 per cent of non-white persons showed frank progression. An additional 25 per cent and 14 per cent of white and non-white persons, respectively, had slight progression. Regression, with or without subsequent stabilization, occurred in about one-fourth of the minimal group in white, and less frequently in non-white persons. Complete stability was observed in only 4 instances out of a total of 190 cases with minimal lesions.

An important index of the degree and severity of progression of the disease is the development of cavity. In the minimal group shown in table 1, progression with roentgenologically demonstrable cavitation was observed in 62 instances, or in 33 per cent. In non-white patients this occurred more frequently than in white patients. Nearly half of non-white persons with initial lesions of minimal extent subsequently developed a cavitary lesion, whereas among white persons this was noted in 28 per cent of the cases.

These observations indicate that the incipient lesion of pulmonary tuberculosis of minimal extent is almost invariably of unstable character, and that it possesses a great tendency to progressive and destructive disease, which is greater in non-white than in white persons.

There was no apparent relation between the location of the incipient small lesion and its subsequent behavior. Progression was just as frequent among cases in which the initial lesion was situated in the supraclavicular or apical area, as in those in which it was located in the subclavicular region. Nor did the progress of the disease in these cases seem to be influenced by the character of the lesion as it appeared in the roentgenogram. It has previously been mentioned (1) that, in the majority of cases with early minimal tuberculosis, the lesion is of the "soft" infiltrative, predominantly exudative type and that the number of cases with discrete nodular, presumably productive lesions was rather small. There was, however, no essential difference noted between these two types of lesions as far as their tendency to progression was concerned.

In the group of cases classified as moderately advanced at the time of initial diagnosis, frank progression of the disease occurred in about half of the patients and there was no significant difference in this regard between white and non-white individuals. It should be pointed out in this connection that the figures for the moderately advanced group probably do not represent the spontaneous trend of the disease that may be expected in this type of case. A large number of those patients had received treatment within a short time after detection of the lesion, including collapse therapy with subsequent control of the pulmonary lesion.

In the far advanced group, all of the non-white patients and all but one of the white patients showed evidence of frank progression of the disease during the period of observation.

Thus far, progression of the lesion was considered on the basis of its behavior during the period of observation. This method has definite limitations when one deals with variable lengths of observation. A more precise way of determining the risk of progressive disease is by a simplified method of life table analysis in

which the population base may be expressed as units of time, or years of observation, for each individual after the initial diagnosis. This method was used for calculating cumulative rates of progression at the end of each year of observation.

This analysis includes only cases in which the lesion was of minimal extent at the time of its initial detection. For cases with moderately advanced lesions true rates could not be calculated because of therapeutic intervention in a large number of these patients, as mentioned above. In the far advanced group nearly all patients showed frank progression of the disease within a short time after the initial diagnosis.

TABLE 2

*Frank progression rates during five years after initial diagnosis of minimal tuberculosis for white and non-white persons*

YEARS AFTER DIAGNOSIS	AVERAGE NUMBER PERSONS AT RISK*	NUMBER WITH FRANK PROGRESSION	PER CENT WITH FRANK PROGRESSION	CUMULATIVE PER CENT WITH FRANK PROGRESSION
White				
1	153.0	39	25.5	25.5
2	107.5	17	15.8	37.3
3	67.5	11	16.3	47.5
4	42.5	5	11.8	53.7
5	28.0	3	10.7	58.7
Non-white				
1	40.5	16	39.5	39.5
2	21.0	4	19.0	51.0
3	13.0	5	38.5	69.9
4	5.0	3	60.0	88.0
5	1.0	0	0.0	88.0

\* Patients showing frank progression cease to be a part of the population after progression has been noted.

Inasmuch as the data mentioned before have indicated that some progression of the lesion was observed in the majority of the cases with incipient lesions of minimal extent, the analysis includes only those cases in which there was *frank progression*, according to the definition indicated above. Because the number of cases observed longer than five years was relatively small, this analysis was limited to a five-year period after the initial diagnosis. Table 2 shows the percentage of cases with frank progression of the disease in the originally minimal group, for each year of observation and cumulative percentages. These data are presented graphically in chart I. It will be noted that the risk of progression to an advanced stage of the disease was great in these cases. At the end of five years, white patients had shown frank progression in about 59 per cent and in non-white persons the progression rate amounted to as much as 88 per cent.

The data presented in table 2 and in chart I also indicate that in white patients the risk of frank progression was greater during the first year after the initial detection of the lesion than in succeeding years. There was, however, a continued risk of progression of the original minimal lesion throughout subsequent years. In a considerable proportion of these cases the first frank progression did not occur until the third to fifth year of observation, after varying periods of instability of the lesion. Among non-white persons, 51 per cent had shown progression by the end of the second year. Although the number of non-white patients in whom no progression occurred during the first two years and who had

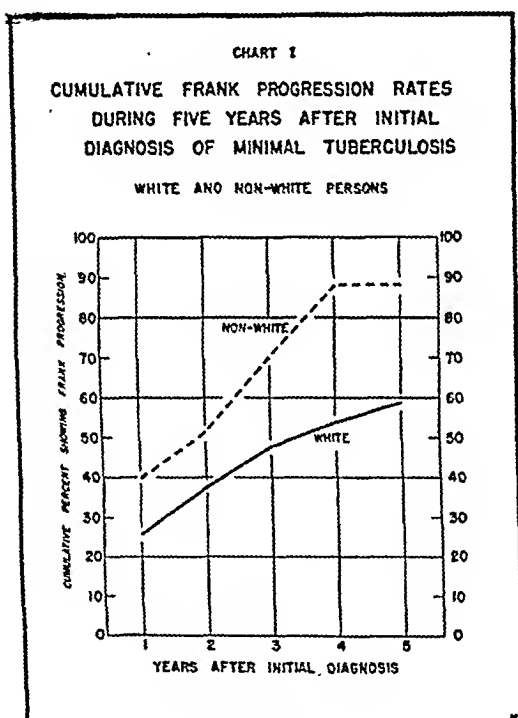


CHART I

remained under continuous observation was rather small, it is evident that the risk of progression persisted during subsequent years.

*Regression:* Generally speaking, regression of the tuberculous lesion may be regarded as a favorable trend in its evolution. Whether this favorable trend is maintained or whether it is merely a transient phase, can be determined only through observation of the subsequent course of the disease. This is of particular importance when one deals with early lesions of minimal extent.

In the total minimal group, some type of regression occurred in 166 cases during the follow-up period. However, only in 71 cases, or in less than half, did the regression result in eventual stabilization of the lesion. In about one-third of this group, initial regression was followed by either frank or slight progression, and in the remaining cases the lesion continued to regress and was con-



sidered as still unstable at the end of the observation period. These data are further indications of the essential instability of the incipient tuberculous lesion.

Regression occurred either by apparently complete or partial absorption of the lesion, by combination of resolution and organization with fibrosis, and in a small number of cases by organization with fibrosis and calcification. The most frequent form of regression was the combination of absorption with apparent organization and fibrosis of the residual lesion. The number of cases in each of these categories was not large enough to indicate whether one form of regression had a more favorable effect on the subsequent course of the disease than another.

*Bacteriological findings:* Examination for tubercle bacilli is a most important aid in determining the course of the disease. In order to evaluate properly the results of such examinations and to correlate them with the clinical and roentgenological findings, it is essential that the frequency and methods of bacteriological studies be reasonably uniform. Owing to the fact that reports on such examinations were obtained from numerous sources and because of the limitations previously indicated (1), these requirements were not fulfilled in this study. For this reason, the data are not suitable for a detailed analysis. It may be of interest, however, to summarize some of the essential findings.

In 191 patients, out of a total of 322, in whom examinations had been performed, or in 59 per cent, tubercle bacilli were demonstrated during the follow-up period. Of these, about half showed positive results within the first few months after the initial diagnosis and, in the remainder, tubercle bacilli were found during the subsequent observation period. By the end of the first year after the initial demonstration of the lesion, positive findings were observed in about 50 per cent of the cases. At the end of the second year the proportion had increased to 55 per cent, and only a relatively small number of additional cases became positive during succeeding years.

In the majority of the cases positive results were obtained through examination of sputum, either by direct smear or concentration, or from concentrated specimens of gastric contents. In only a few cases was the culture method employed; and animal inoculations were practically not done at all. The percentage of cases with positive bacteriological findings in this series probably represents a minimum figure, which would in all likelihood be considerably larger had more exacting methods of examination been used throughout.

Patients in whom the disease was far advanced at the time of the first diagnosis, all had positive findings. Of those with moderately advanced lesions, tubercle bacilli were demonstrated during the course of observation in 75 per cent. As to patients with initial lesions of minimal extent, it has previously been mentioned (1) that 20 per cent of those in whom bacteriological examination had been carried out during the early period of observation had positive findings. There were 178 cases with originally negative findings or with no examination performed during that period. Of these, subsequent examinations revealed tubercle bacilli in 70 cases, or in 39 per cent. In the majority of these cases the positive findings coincided with a frankly progressive behavior of the pulmonary lesion. The lack of suitable data did not permit a more detailed analysis of the

bacteriological findings and their relation to the behavior of the incipient minimal lesion.

*Relation of age to behavior of the lesion:* To what extent is the age of the patient a significant factor in influencing the behavior of the incipient lesion of pulmonary tuberculosis, especially in cases with early minimal involvement? The majority of the patients with minimal lesions, about three-fourths, were under 25 years of age when the lesion was first detected. One-fourth of the patients were 25 years of age or older. For the purpose of comparison, the cases were divided into two broad age-groups, namely, 10 to 24 years, and 25 years and over. The median age for the group 10 to 24 years was 18 years, and for the group 25 years or older it was 30 years.

TABLE 3

*Frank progression rates during five years after initial diagnosis of minimal tuberculosis by age*

YEARS AFTER DIAGNOSIS	AVERAGE NUMBER PERSONS AT RISK*	NUMBER WITH FRANK PROGRESSION	PER CENT WITH FRANK PROGRESSION	CUMULATIVE PER CENT WITH FRANK PROGRESSION
Under 25 Years of Age				
1	145.0	41	28.3	28.3
2	88.5	13	14.7	38.8
3	63.0	14	22.2	52.4
4	36.5	6	16.4	60.2
5	23.5	3	12.8	65.3
25 Years of Age and Over				
1	49.5	14	28.3	28.3
2	29.5	8	27.1	47.7
3	16.5	2	12.1	48.8
4	9.0	3	33.3	65.8
5	3.5	0	0.0	65.8

\* Patients showing frank progression cease to be a part of the population after progression has been noted.

Table 3 shows the percentages of cases with frank progression in these two age-groups, for patients in whom the initial lesion was minimal, calculated on the basis of person-years of observation. Since the numbers of non-white persons in the two age-groups were small and since preliminary analyses by age indicated no significant difference between white and non-white persons, the data for the two groups have been combined in this table. It may be seen from the figures that the progression rates were practically the same for patients 10 to 24 years of age as for those 25 years or older. These data indicate that age, as such, had no definite influence over the behavior of the incipient tuberculous lesion, and that its potentialities for progression to manifest clinical disease are great regardless of the age of the patient.

*Treatment and its effect on behavior of the lesion:* In considering treatment and its effect on the subsequent behavior of the lesion, it is essential to separate cases

with early lesions of minimal extent from those cases in which the lesion was in an advanced stage at the time of its initial detection.

Of the cases included in the minimal group, 71 per cent had institutional treatment some time during the period of observation. Thirty-eight per cent received hospital or sanatorium care while the lesion was minimal, the remainder having been admitted for institutional treatment for the first time after frank progression of the lesion had occurred. However, only one-third of the cases with originally minimal lesions had a period of sanatorium care which was judged as adequate, generally for six months or longer. The remaining patients of this group were considered as having received no institutional treatment for their minimal lesions, although a small number of them had been in sanatoria for short periods of time, but had left against medical advice. In explanation of the fact that this group contains a rather large proportion of "untreated" cases it should be mentioned that this was due partly to the reluctance of many patients with minimal asymptomatic lesions to accept sanatorium treatment, and partly to the failure on the part of some physicians to insist on such care.

Among patients who had received sanatorium care, frank progression of the minimal lesion was observed in 28 per cent of the cases. Although in a considerable number of additional patients of the treated group, slight progression of the lesion was noted during the period of observation, this did not result in obvious extension of the disease. Among patients who had no institutional treatment, frank progression occurred in 67 per cent of the cases. A favorable behavior of the lesion, as indicated by regression resulting in stabilization, or by continuous regression, was observed twice as frequently in patients who had received sanatorium treatment as in those without such care. With rare exceptions, the type of treatment consisted of routine sanatorium care, collapse therapy having been employed in only a few cases for the control of lesions of minimal extent.

Forty-nine patients with initial lesions of minimal extent who subsequently showed frank progression of the disease, later received some form of collapse therapy, either pneumothorax or thoracoplasty. Arrest of the disease or control of the lesion under continued pneumothorax treatment was obtained in about 43 per cent of the cases.

In evaluating the effect of treatment, especially the effect of sanatorium care without collapse therapy, on the subsequent course of the disease in cases with incipient minimal lesions, great caution must be exercised in the interpretation of the available data. A group of patients that had received sanatorium treatment cannot be compared with one that had no such care without giving consideration to a number of important factors which may greatly influence the composition of each of the two groups. The fact that one group of patients readily accepts and carries out the recommended treatment, while the other declines to heed the physician's advice, constitutes a selective factor which is bound to limit their comparability. Two such groups of persons are likely to differ in many other respects, such as their general attitude towards the disease, their mode of life, and other factors which may well affect the subsequent behavior of the lesion. It

must also be pointed out that the data concerning the type of institutional care and duration of treatment are by no means comparable, as this group includes patients who had received treatment in a number of institutions with various standards of sanatorium regimen.

Because of these limiting factors it was not possible to determine to what extent sanatorium treatment actually influences the subsequent behavior of the early tuberculous lesion of minimal extent. However, the data presented here do indicate that patients who had received sanatorium treatment fared considerably better than those without such treatment. While it is true that in a certain proportion of untreated patients the lesion showed a favorable behavior, this trend was observed more frequently in those who had had an adequate period of institutional treatment. At the same time it may be pointed out that in the latter group an appreciable number of the cases showed frank progression of the disease subsequent to completion of the sanatorium treatment. In this connection it may be mentioned that, according to the available information, the majority of the patients received routine institutional care without any extended period of strict bed-rest. The question may be raised to what degree a more rigid rest regimen, as particularly emphasized by Amberson (2), might have influenced the results of treatment in a more favorable way.

A discussion of the treatment and its results in moderately advanced or far advanced cases at the time of initial detection of the lesion is omitted here, as this question has no direct bearing on the problem of incipient pulmonary tuberculosis.

#### STATUS AT THE END OF THE OBSERVATION PERIOD

*Stage of disease and activity:* The condition of the patient on termination of the observation period provides significant information on the progress of the disease. These data are shown in table 4 in which the cases are classified according to the stage of the disease on initial diagnosis, and the state of disease and activity on last observation. It will be noted that, at the end of the observation period, about half of the white patients and two-thirds of the non-white patients were classified as having active disease. Slightly less than half of the white group and one-third of non-white persons had reached either a stage of arrest or apparent cure of the disease, or control of the lesion under pneumothorax treatment.

The seriousness of the early lesion of minimal extent is indicated by its status at the end of the observation period. Among white individuals, 34 per cent had either moderately advanced or far advanced active disease. In an additional 11 per cent, the lesion had progressed to a moderately advanced or far advanced stage, but subsequently became either arrested or controlled under pneumothorax therapy. Among non-white patients with originally minimal lesions, 41 per cent had either moderately advanced or far advanced active disease by the end of the follow-up period, and in an additional 23 per cent, who had progressed to an advanced stage of the disease, the lesion later became either arrested or controlled with pneumothorax.

In cases with an original diagnosis of moderately advanced disease, the percentages of patients with active and inactive lesions at the end of the observation period was essentially the same in white as in non-white patients. It seems significant, however, that among white patients with an initial diagnosis of far advanced disease, some cases had reached an inactive status, while nearly all non-white patients of this category remained active throughout the observation period. In 3 cases with initial lesions of chronic pulmonary tuberculosis, acute

TABLE 4

*Distribution of cases of pulmonary tuberculosis according to stage of disease and activity at the end of observation, by initial diagnosis, for white and non-white persons*

LAST DIAGNOSIS	TOTAL		INITIAL DIAGNOSIS*					
			Minimal		Moderately advanced		Far advanced	
	White	Non-white	White	Non-white	White	Non-white	White	Non-white
Number of cases								
Total.....	220	82	152	39	55	25	13	18
Per cent								
Total.....	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Active.....	51.4	65.9	50.7	61.5	49.1	52.0	69.2	94.4
Minimal.....	11.4	9.8	15.8	17.9	1.8	4.0	0.0	0.0
Moderately advanced.....	15.9	11.0	17.1	17.9	16.4	8.0	0.0	0.0
Far advanced.....	23.6	42.7	17.1	23.1	30.9	36.0	69.2	94.4
Acute miliary tuberculosis.....	0.5	2.4	0.7	2.6	0.0	4.0	0.0	0.0
Arrested, apparently cured, or controlled with pneumothorax	48.6	34.1	49.3	38.5	50.9	48.0	30.8	5.6
Minimal.....	30.5	15.8	38.1	15.4	16.4	28.0	0.0	0.0
Moderately advanced.....	14.5	14.6	9.2	18.0	32.7	20.0	0.0	0.0
Far advanced.....	3.6	8.7	2.0	5.1	1.8	0.0	30.8	5.6

\* Does not include 2 cases of miliary tuberculosis, 2 cases of active primary tuberculosis, and 38 living patients with less than one year observation.

miliary tuberculosis had developed during the follow-up period. One of these patients was white and 2 were non-white.

**Mortality:** Of the 344 cases, 62 patients have died of tuberculosis. Among 253 white patients, death occurred in 27 cases, or in 10.7 per cent, and of 91 non-white patients, 35, or 38.5 per cent, died during the period of observation. Of 75 Negroes included in the non-white group, 30 died, 4 deaths occurred among 13 Puerto Ricans, and one death in a person of other non-white racial stock.

Table 5 shows fatality rates calculated on the basis of person-years of obser-

vation, according to the stage of disease at the time of the initial diagnosis, for white and non-white persons. It is apparent that the case fatality rate was much higher among non-white than among white patients, the ratio being approximately 4.5 to 1. In both white and non-white persons the fatality rate increased with the increase in extent of the disease at the time of initial diagnosis. The fatality rate was consistently higher in the non-white group. In the minimal category the rate was almost four times as great in non-white as in white individuals. In those with moderately advanced lesions the ratio was 3 to 1, and in the far advanced group it was more than 4 to 1.

The fatality rate was about the same for males as for females among white persons. In the non-white group the rates were higher for females. Because of the small numbers of cases in the individual categories according to the stage of

TABLE 5

*Fatality among patients with pulmonary tuberculosis, according to stage of disease on initial diagnosis, for white and non-white persons\**

STAGE OF DISEASE AND COLOR OF PATIENT	PERSON-YEARS AT RISK	NUMBER OF DEATHS	RATE PER 100 PERSON-YEARS
White.....	935	27	2.9
Minimal.....	639	11	1.7
Moderately advanced.....	255	8	3.1
Far advanced.....	41	8	19.5
Non-white.....	249	33	13.3
Minimal.....	144	9	6.3
Moderately advanced.....	87	8	9.2
Far advanced.....	18	16	88.9

\* Does not include 2 deaths from miliary tuberculosis.

disease, the statistical significance of the difference between non-white males and females could not be proved.

Further information concerning the tempo of progression of the disease and its eventual outcome may be obtained by determining fatality rates in relation to the time interval from the initial demonstration of the lesion to fatal termination. This was done for 248 cases in which the interval from the normal roentgenogram to the first detection of the lesion ranged from one to twelve months, as it seemed that this group would be of particular interest from the standpoint of early development of pulmonary tuberculosis. The fatality rates were calculated on the basis of person-years of observation and the data are presented in table 6 and in chart II, separately for white and non-white persons.

Among 188 white patients in this group there were 16 deaths, and of 60 non-white patients 19 died. It will be noted that among white persons there was only one death during the first year after the initial diagnosis, the case fatality rate

TABLE 6

*Fatality among 188 white and 60 non-white patients with pulmonary tuberculosis diagnosed within one year of a normal X-ray by length of observation*

YEARS AFTER INITIAL DIAGNOSIS	INDIVIDUAL YEAR			CUMULATIVE YEARS		
	Average persons at risk	Number of deaths	Rate per 100 person-years	Average persons at risk	Number of deaths	Rate per 100 person-years
White						
1	162.5	1	0.6	162.5	1	0.6
2	145.0	4	2.8	307.5	5	1.6
3	116.5	3	2.6	424.0	8	1.9
4	77.5	3	3.9	501.5	11	2.2
5	63.0	3	4.8	564.5	14	2.5
Over 5	68.5	2	2.9	633.0	16	2.5
Non-white						
1	51.5	11	21.4	51.5	11	21.4
2	38.5	2	5.2	90.0	13	14.4
3	31.0	2	6.5	121.0	15	12.4
4	24.0	2	8.8	145.0	17	11.7
5	15.5	1	6.5	160.5	18	11.2
Over 5	15.5	1	6.5	176.0	19	10.8

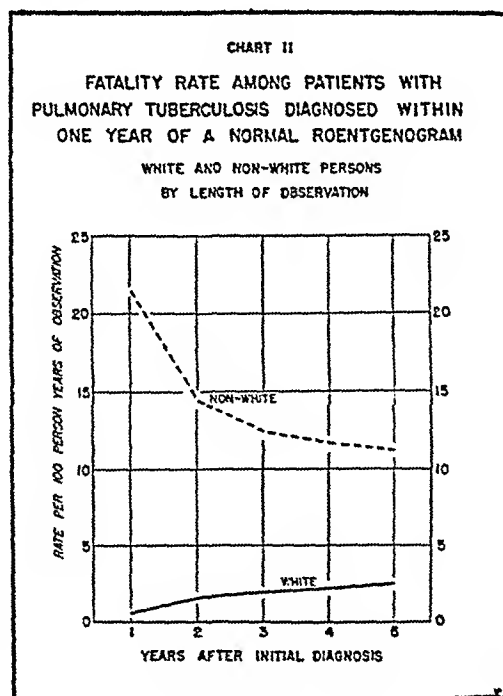


CHART II

amounting to 0.6 per hundred person-years, and that the rates increased during the first five years. In non-white individuals, on the other hand, the fatality rate during the first year was excessively high, amounting to 21.4 per hundred person-years. More than half of all deaths among non-white patients occurred during the first year. The rates were much lower in this group in subsequent years, without significant variation for each succeeding year. They were consistently higher, however, throughout the years of observation than the rates among white persons.

The fatality rates for the whole period of observation for the 248 patients in whom pulmonary tuberculosis had developed within one year of a normal roentgenogram were slightly lower in both white and non-white persons than the rates for the entire material shown in table 5. However, an analysis by increasing periods of observation shows a striking difference between white and non-white individuals. In white patients the rate increased from 0.6 per hundred person-years at the end of the first year of observation to a rate of 2.5 at the end of five years, while in non-white patients it decreased from 21.4 to 11.2 per hundred person-years during the corresponding period. This difference is caused by the averaging of the high fatality rate among non-white persons in the first year of observation, with the much lower rates during succeeding years, while in white persons the reverse pattern is observed. These data further emphasize the much greater severity of the disease in the non-white group, as compared with white persons.

#### DISCUSSION

There is ample evidence that extensive pulmonary tuberculosis may develop in an individual without a previously recognizable lesion within a short period of time, in some cases even within a period of a very few weeks. Such cases tend to emphasize the distinction that must be made between "early," in point of time, and the anatomical extent of the lesion. While in those cases the lesion is of recent origin, yet, because of the extent of involvement, it would not seem proper to consider them as "incipient," in the usual sense of the word.

Of particular importance are the cases showing lesions of recent origin in which the involvement is of limited extent. Experience indicates that the majority of these patients have no symptoms and that in most instances such lesions are found on routine roentgenographic examination. Therefore, in commenting on the behavior of the initial tuberculous lesion and on the evolution of the disease, the attention will be focused chiefly on the early lesion of minimal extent.

The present observations indicate that the incipient lesion of pulmonary tuberculosis of limited extent is practically always of unstable character and that in a large proportion of the cases it progresses to advanced and destructive disease. There is reason to believe that the majority of cases of manifest clinical tuberculosis have their origin in these seemingly inconspicuous, small lesions.

Although extensive progression may set in within a short time after the initial appearance of the lesion, this is not the usual behavior. More often frank pro-



gression is preceded by varying periods of instability of the lesion, such as slight progression alternating with regression, or *vice versa*. In many cases obvious progression to manifest disease does not occur until several years after the first demonstration of the lesion. This is a further indication that the inherently unstable character of a lesion that had developed during observation may persist for long periods of time. On the other hand, uninterrupted regression of the initial lesion, followed by stabilization, usually signifies a favorable behavior. It cannot be stated, however, what minimum period of stability may be regarded as a reasonable indication of a continued stable behavior.

On the basis of the findings in this series, it was not possible to determine any definite criteria which might enable one, from the outset, to prognosticate the subsequent evolution of the incipient minimal lesion. The age of the patient did not appear to be of much significance insofar as the frequency of progressive disease was concerned. Neither did the location or the roentgenological character of the initial lesion offer dependable guides for determination of its future behavior. Intensive and systematic examinations for tubercle bacilli may be helpful in some cases. There is reason to believe, however, that a great many of the truly beginning small lesions are not likely to yield positive bacteriological findings, even with the most exacting methods of examination.

The one point which deserves particular consideration is the racial factor. Consistent differences between white and non-white individuals were noted in this material, both with regard to the mode of onset and subsequent progress of the disease. The frequent acute beginning and rapid spread of the lesion, observed among non-white patients, has been referred to earlier (1). Among cases in which the early lesion was of minimal extent when first detected, progression was more frequent in non-white than in white persons. Above all, the greater severity of the disease in the non-white group is indicated by a much higher case fatality rate and shorter duration of illness from the time of initial detection of the lesion to death, as compared with white persons. The usually insidious beginning and typically chronic course of pulmonary tuberculosis are more characteristic for the behavior of the disease in white than in non-white persons. These observations are in accord with the findings of Pinner and Kasper (3) who have studied the pathological peculiarities of tuberculosis in the American Negro.

The data here reported offer further evidence that it is the high case fatality rate in Negroes, rather than a greater prevalence of the disease, which is chiefly responsible for their greatly disproportionate death rate from tuberculosis, as compared with the white population. The case fatality rate observed in this material was four times as great in non-white as in white persons. This ratio closely corresponds with current tuberculosis mortality figures reported in this country, which indicate a rate about four times as high for the non-white as for the white population.

The present findings have indicated that incipient pulmonary tuberculosis has a serious prognosis. A large percentage of cases with minimal initial lesions have shown progression to manifest clinical disease during the period of observation.

In an additional substantial proportion of the cases, progression to an advanced stage had occurred prior to the initial demonstration of the lesion and within a relatively short time after a normal roentgenogram had been obtained. The question arises whether this behavior of the early lesion may be considered as typical for incipient pulmonary tuberculosis as a whole.

The material of this study does not represent a random sample of the population, as it consists almost entirely of persons who had been under observation because of a history of contact with a known case of tuberculosis. In view of the selected character of this group, special consideration must be given to two important factors, namely, exposure to infection and particular susceptibility to the disease. Although the available data were not suitable for a detailed evaluation of the epidemiological conditions, there was but little question that the majority of the persons in this group had been in intimate and prolonged contact with open cases of pulmonary tuberculosis, in most instances with a member of their immediate family. While it is not possible to assess the relative importance of exposure and familial susceptibility, the indications are that a combination of these two factors constitute an especially unfavorable set of circumstances. Recent studies of Puffer (4) on familial tuberculosis, and of Kallmann and Reisner (5) on tuberculosis in twins, have again emphasized the significance of hereditary factors in the pathogenesis of tuberculosis.

It is obviously impossible to determine to what extent those special conditions peculiar to this particular group, may have influenced the behavior of the incipient lesion in an unfavorable manner. To what degree these observations may have general validity, would have to be determined by a study of development of pulmonary tuberculosis from its incipency in a group of persons more nearly representative of the general population.

The available data did not meet the requirements for an accurate evaluation of the effect of sanatorium care on the subsequent course of the disease in cases with minimal early tuberculous lesions. The findings did indicate, however, that institutional treatment without collapse therapy has apparently been beneficial in a considerable percentage of patients. Controlled studies under suitable conditions are needed in order to provide an answer to some of the basic questions in connection with the therapeutic management. It would be of particular interest if it could be determined what period of institutional treatment may be regarded as the required minimum or optimum. There is also the important question as to how much more lasting benefit may be derived from a rigorous rest regimen, as compared with a less restricted routine type of sanatorium regimen, a point on which there is at present considerable disagreement.

Patients with incipient tuberculous lesions of limited extent require not only careful therapeutic management at the time the lesion is first detected but intensive and prolonged follow-up observation as well. The observations concerning the behavior of the early minimal lesion indicate that the tendency to progression may persist for long periods of time after its initial appearance.

## ILLUSTRATIVE EXAMPLES

FIG. 1. Female, white, age 13. Roentgenogram on May 13, 1942 showed pleural effusion at the left base, no other abnormal findings. On December 9, 1942 (A) a very small density was noted in the lateral portion of the right second anterior interspace, just above the third rib (sides are reversed in these reproductions). On February 27, 1943 (B) the area of infiltration in the second interspace had become distinctly larger. Gastric examination was positive for tubercle bacilli. Treatment was refused by patient. On August 18, 1947 (C) there was extensive bilateral progression of the lesion.

FIG. 2. Female, Negro, age 31, contact. Roentgenogram on January 29, 1940 was normal. The film of May 16, 1941 (A) showed an ill-defined small density within the shadow of the fifth right posterior rib (sides are reversed in these reproductions). On May 1, 1942 (B) a definite cavity was noted in that area. Subsequently, disappearance of cavity and apparent absorption of the lesion. Film of July 1, 1946 (C) showed essentially normal findings.

FIG. 3. Female, Negro, age 26, contact. Roentgenogram on July 14, 1942 was normal. Subsequent film of January 30, 1943 (A) demonstrated an area of soft infiltration at the summit of the right apex and a small ill-defined density over the lower border of the first right anterior rib (sides are reversed in these reproductions). On March 15, 1944 (B) there was definite progression of the lesion, scattered foci of infiltration extending from the apex to the level of the second anterior rib. On April 26, 1945 (C) there was further extensive progression with multiple cavities. Sputum was positive for tubercle bacilli. Subsequent thoracoplasty has resulted in arrest of the lesion.

FIG. 4. Male, white, age 43, contact. Roentgenogram on May 23, 1946 was normal. On December 13, 1946 the film (A) showed small flocculent densities in the left first anterior interspace and below the second rib. One month later, on January 17, 1947 (B) there was extensive progression of the lesion, with areas suggestive of cavity formation in the lateral portions of the first and second interspaces. Sputum was positive for tubercle bacilli.

FIG. 5. Male, white, age 17, contact. Roentgenogram of September 12, 1934 showed a calcified nodule at the base of the right lung, no other abnormal findings. Follow-up film of November 30, 1935 (A) demonstrated a few small nodular foci in the left apex, partly superimposed over the rib shadow (sides are reversed in these reproductions). On April 11, 1936 (B) there was definite progression of the lesion, disseminated nodular foci extending from the apex to the level of the third anterior rib. Following sanatorium treatment there was marked regression of the lesion with subsequent stabilization. Film of June 25, 1942 (C) showed residual scattered calcified nodules in the apex and first interspace.

FIG. 6. Female, Negro, age 18. A routine roentgenogram of September 5, 1937 was normal. On December 6, 1938 the film (A) demonstrated several small flocculent densities in the outer portion of the left first anterior interspace. On March 16, 1940 (B) there was considerable progression of the lesion with extension of the infiltration through the greater portion of the first interspace and an area suggestive of small cavity. Sputum was positive for tubercle bacilli. Treatment was refused by patient. A roentgenogram on November 3, 1945 (C) showed wide-spread bilateral involvement with extensive excavation of both lungs. Patient died on September 4, 1946.

FIG. 7. Male, white, age 22, contact. Roentgenogram of March 2, 1939 was normal. Six weeks later, on April 15, 1939 (A) areas of confluent soft infiltration were demonstrated in the right apex and first anterior interspace. Sputum was positive for tubercle bacilli. Under sanatorium treatment the lesion has subsequently regressed by apparent absorption. Roentgenogram of March 18, 1940 (B) showed essentially normal findings.

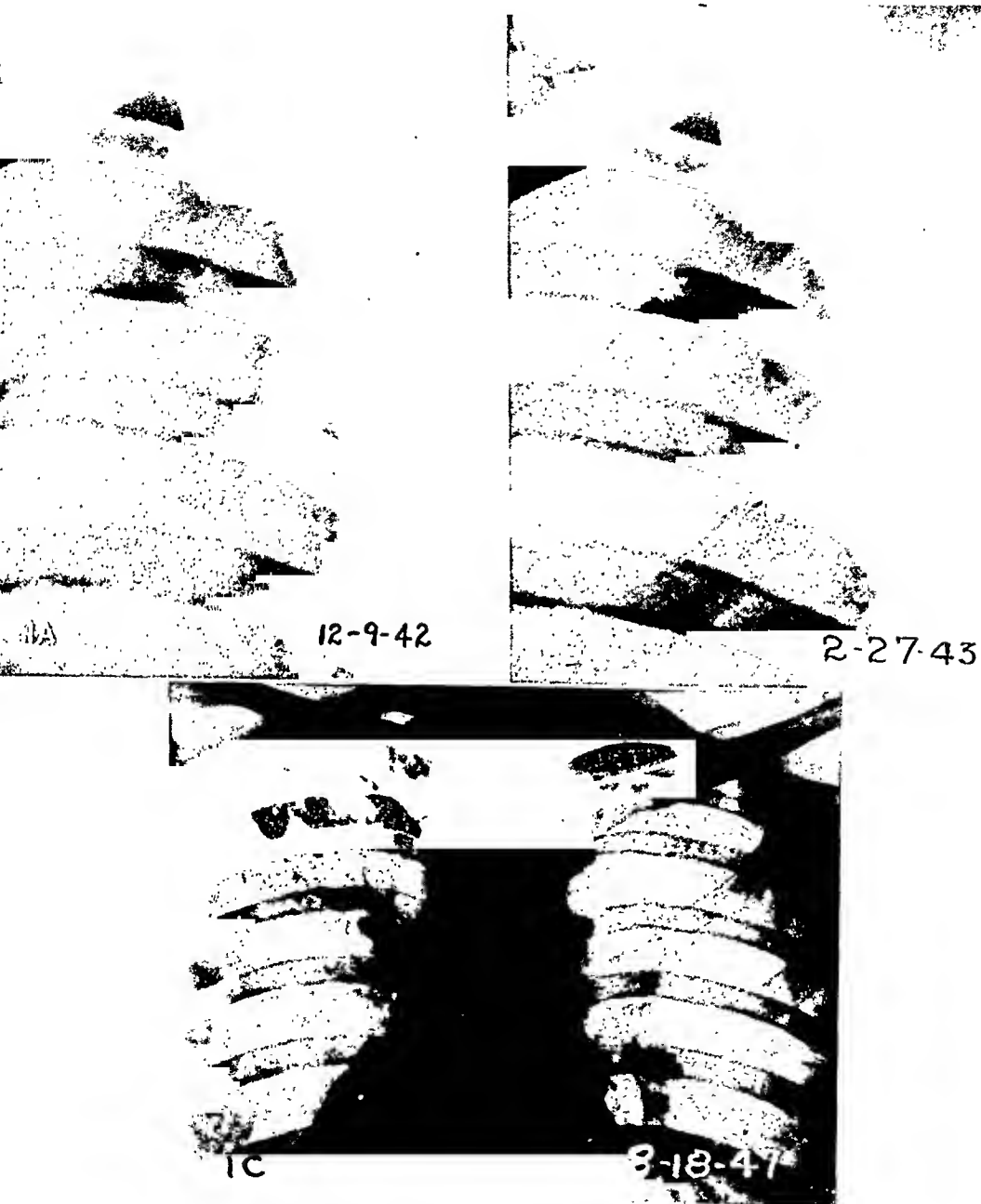


FIG. 1

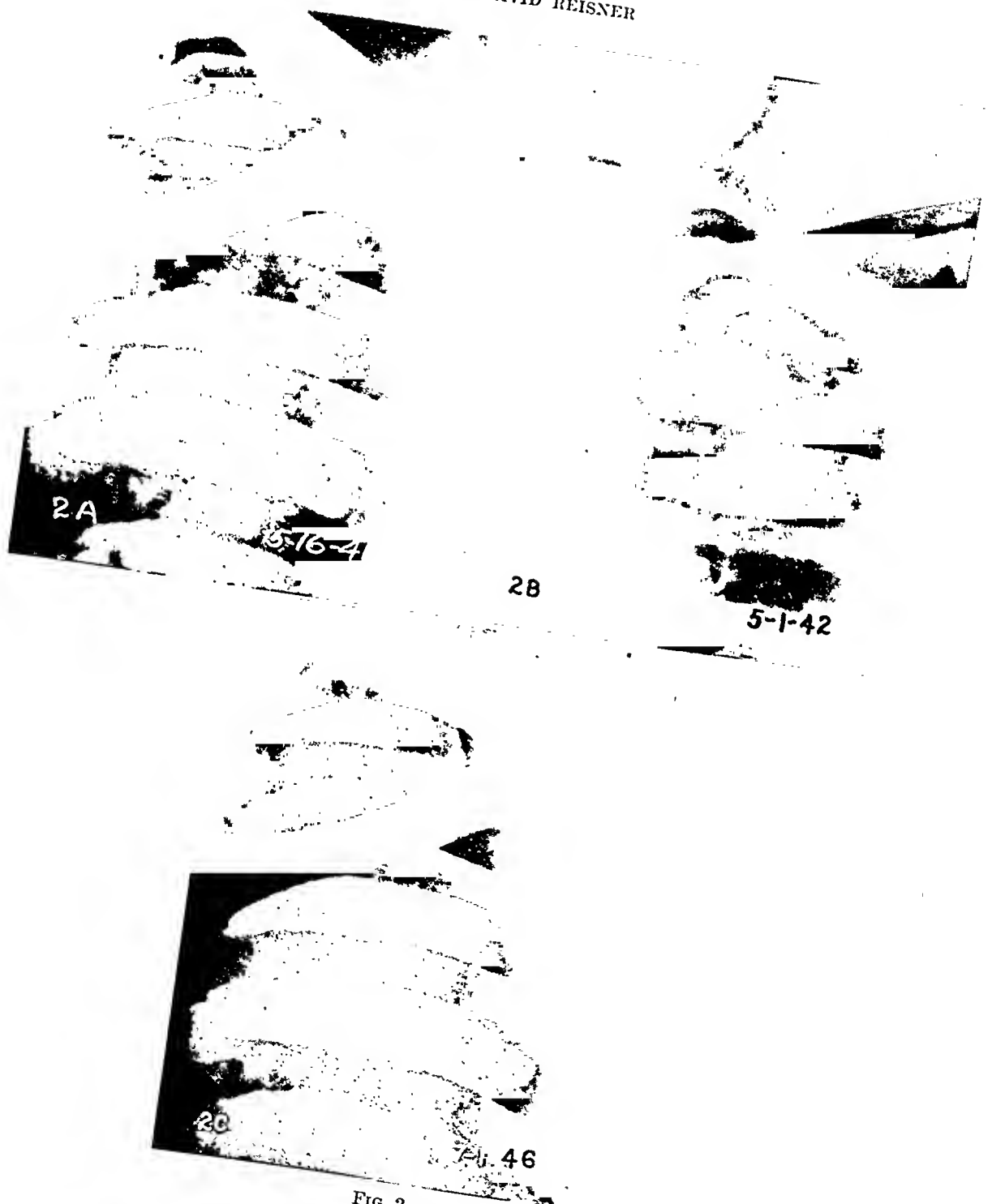


FIG. 2

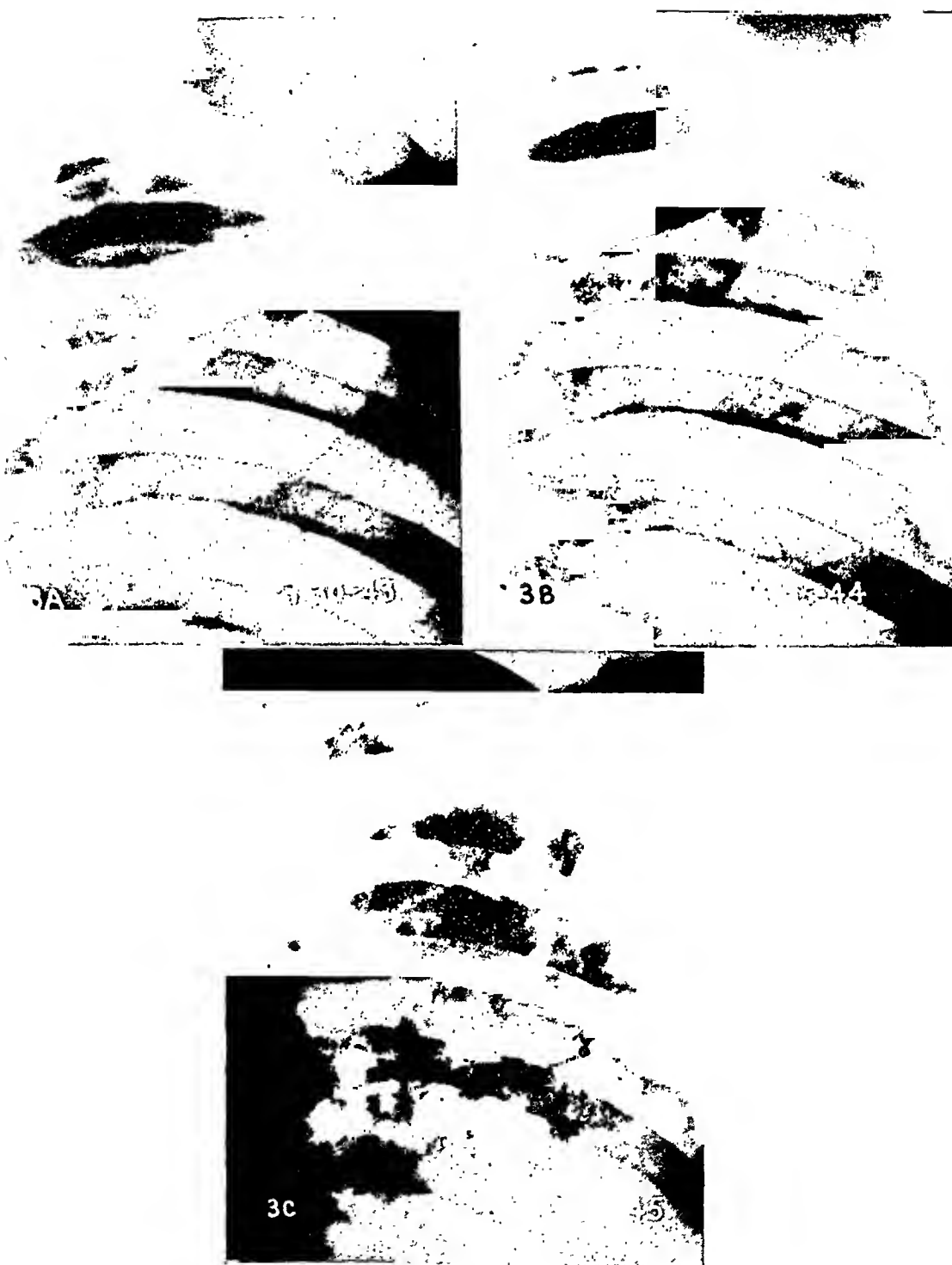


FIG. 3

## SUMMARY

1. The evolution of pulmonary tuberculosis was studied in a group of 340 cases in which roentgenologically demonstrable lesions had developed during the period of observation.

2. The majority of the patients, 69 per cent, were observed for periods ranging from two to ten years after the initial detection of the pulmonary lesion. The remainder of the group were observed less than two years. The average observation period amounted to three years and a half.

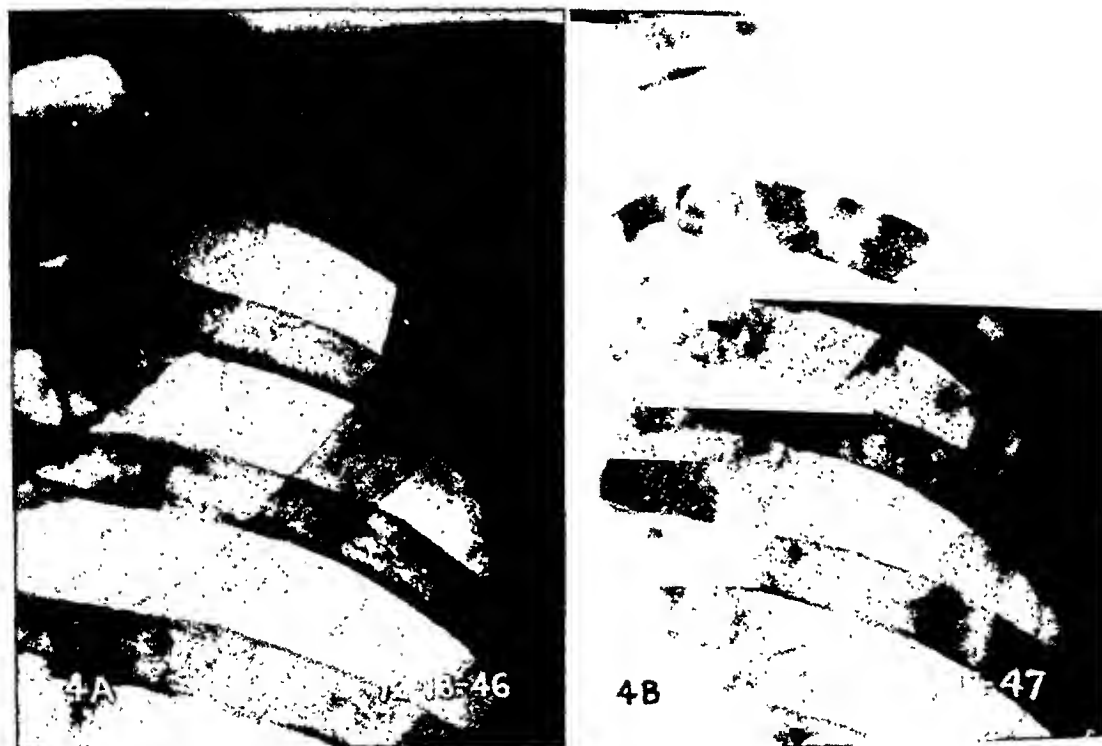


FIG. 4

3. Particular attention was given to the behavior of the incipient lesion of minimal extent. The observations have indicated that these lesions are practically always unstable and that they exhibit a great tendency to progressive disease. The cumulative rate of frank progression, calculated on the basis of person-years of observation, amounted to 59 per cent in white persons, and to as much as 88 per cent in non-white patients.

4. The majority of cases with advanced and destructive forms of pulmonary tuberculosis seem to have their origin in these inconspicuous early minimal lesions.

5. There is apparently no way of predicting the subsequent evolution of the incipient minimal lesion, other than by actual observation of its behavior over a

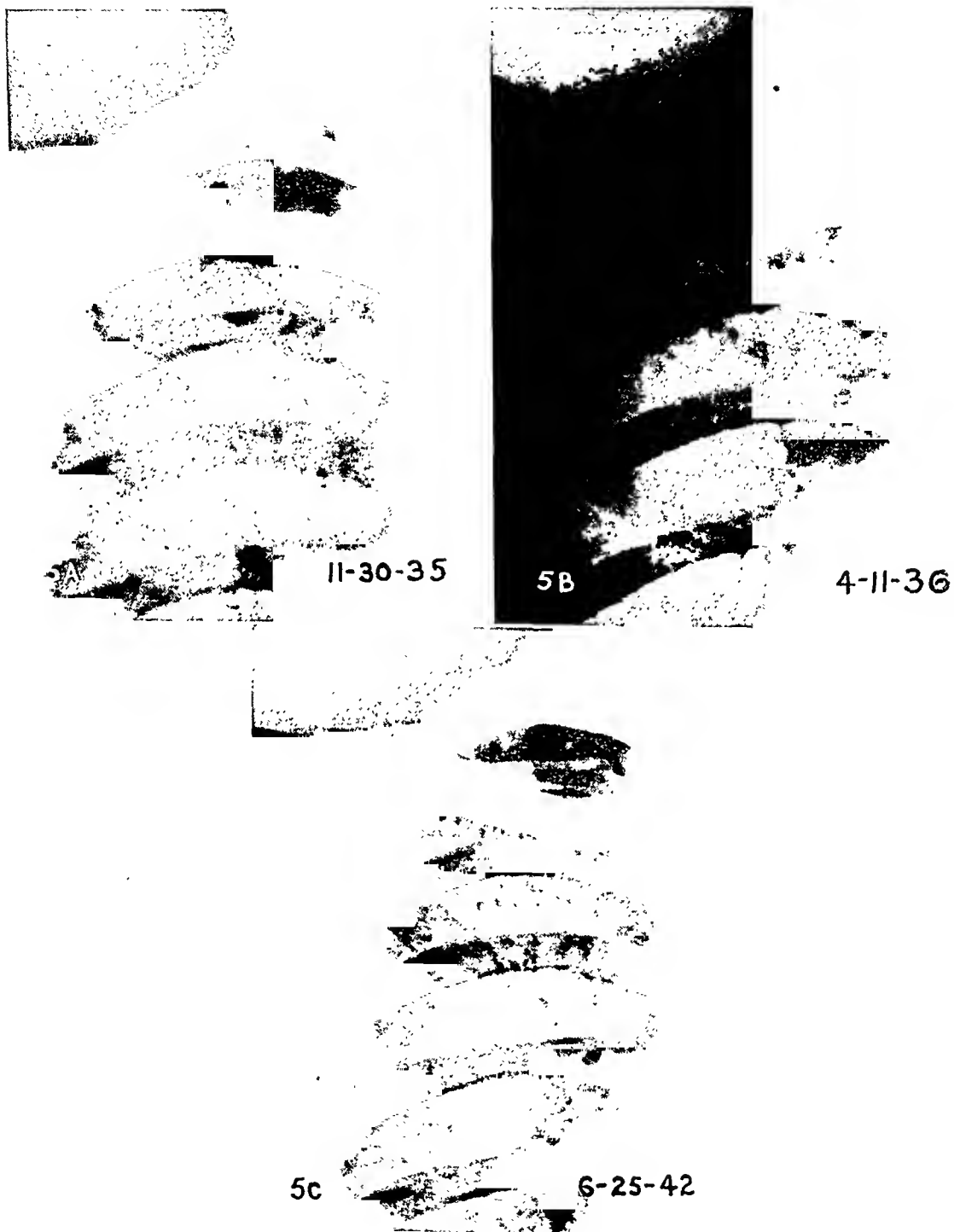


FIG. 5



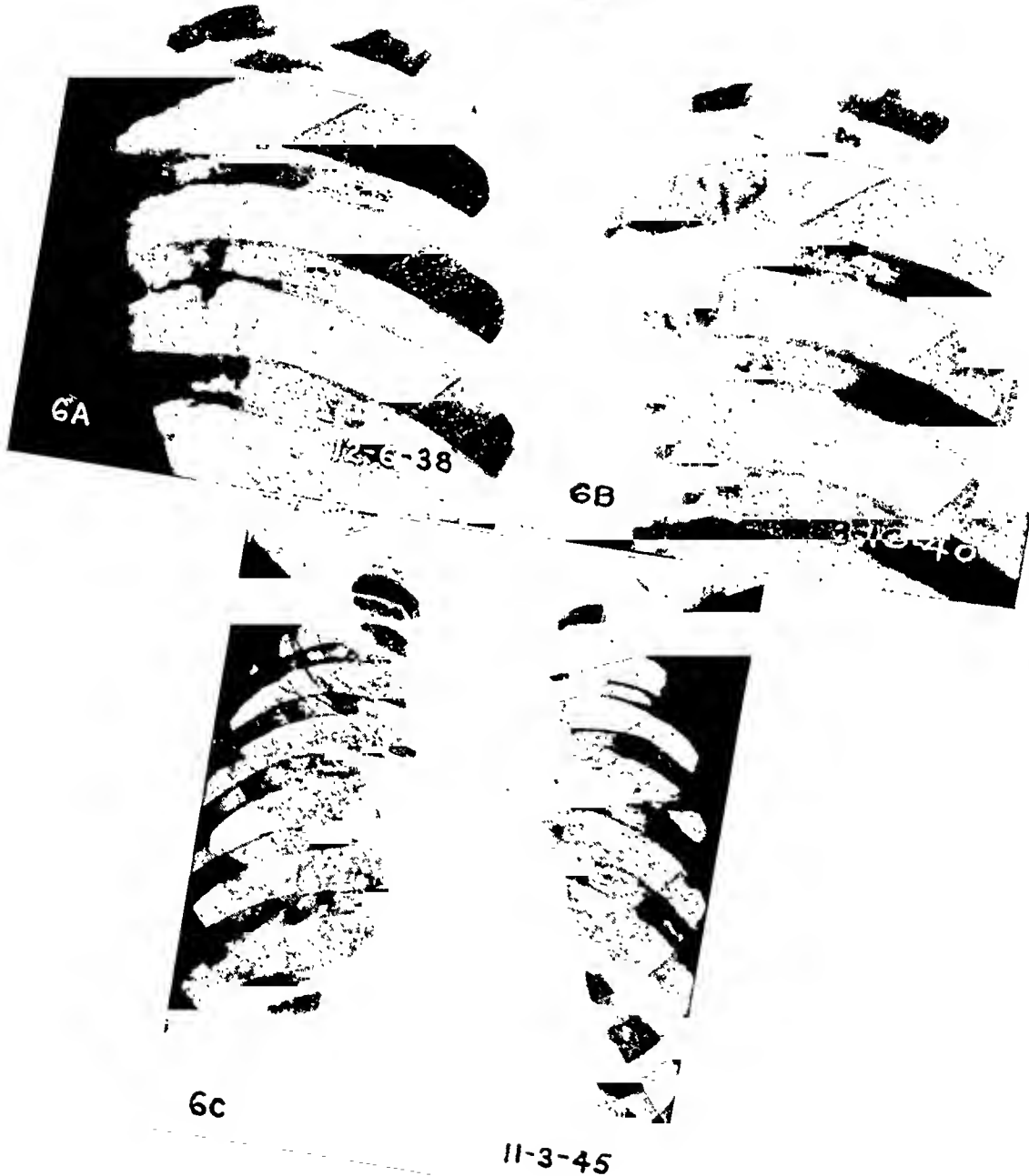


FIG. 6

considerable period of time. Neither the age of the patient, nor the location or roentgenological appearance of the lesion, could be regarded as dependable guides for estimating the relative risk of progressive disease.

6. Consistent differences were observed between white and non-white persons as regards the mode of onset, the course and ultimate outcome of the disease. Its greater severity in the non-white group is indicated by a greater frequency, as well as a more rapid tempo, of progression, and by a case fatality rate four times higher than in white persons.

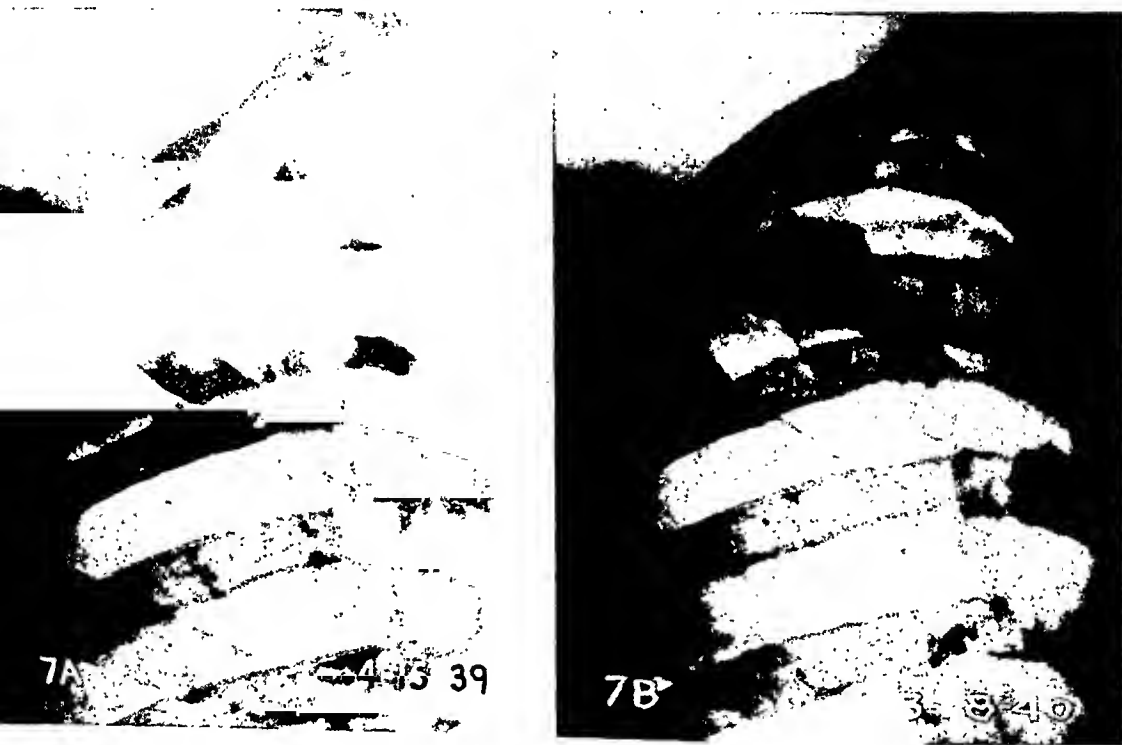


FIG. 7

7. The selective factors peculiar to the material of this study, which consisted largely of familial contacts, have been stressed. The general applicability of the present observations concerning the behavior of the incipient lesion would have to be determined by studies of more suitable population groups.

8. The serious potentialities of minimal incipient lesions of the pulmonary tuberculosis indicate the need for both careful therapeutic management and extended follow-up observation of such cases.

#### SUMARIO

*Ineipiente y Evolución de la Tuberculosis Pulmonar. II. Comportamiento de la Lesión y Marcha de la Enfermedad durante el Período de Observación*

1. En un grupo de 340 casos en que se presentaron durante el período de observación lesiones roentgenológicamente demostrables, se estudió la evolución de la tuberculosis pulmonar.

2. La mayoría, 69 por ciento, de los enfermos fueron observados durante períodos que variaron de dos a diez años a partir del descubrimiento de la lesión pulmonar. El resto del grupo fué observado menos de dos años. El período de observación promedió tres años y medio.

3. El comportamiento de la lesión incipiente de tamaño mínimo fué objeto de estudio especial, indicando las observaciones realizadas que dichas lesiones son casi siempre inestables y manifiestan mucha tendencia a convertirse en enfermedad evolutiva. El coeficiente acumulativo de franca agravación, calculada a base de persona-años de observación, ascendió a 59 por ciento en los blancos, y hasta 88 por ciento en los atros enfermos.

4. La mayoría de los casos con formas avanzadas y destructoras de tuberculosis pulmonar parecen haber tenido su origen en dichas lesiones incipientes y aparentemente insignificantes de tamaño mínimo.

5. Al parecer no hay modo de determinar la evolución subsiguiente de la lesión incipiente mínima, aparte de la observación real de su comportamiento durante un período considerable de tiempo. Ni la edad del enfermo, ni la localización o aspecto roentgenológico de la lesión pueden ser considerados como guías fehacientes para estimar el riesgo relativo de que sobrevenga enfermedad evolutiva.

6. Observáronse diferencias constantes entre los blancos y los no blancos con respecto al modo de iniciación, evolución y resultado final de la enfermedad. La mayor gravedad en los no blancos queda indicada por la mayor frecuencia, así como rapidez, de la agravación, y por la morboletalidad, cuádruple que en los blancos.

7. Los factores selectivos que son peculiares del material de este estudio, que constaba en gran parte de contactos familiares, han sido recalcados. La aplicabilidad general de las observaciones actuales acerca del comportamiento de la lesión incipiente tendrá que ser determinada mediante estudios de grupos de población más adecuados.

8. Las graves potencialidades de la lesión incipiente de la tuberculosis pulmonar de extensión mínima indican la necesidad tanto de cuidadosa atención terapéutica como de prolongada observación subsiguiente en dichos casos.

I wish to express my appreciation and thanks to Mr. George Kerehner, Senior Statistician, and to Mr. Samuel Lubin and Miss Frances Sachs, Junior Statisticians, for their great help in the statistical analysis of the material and in tabulating the data for this and the preceding paper. Miss Marjorie Bellows kindly offered some helpful suggestions for the presentation of the statistical data. Mr. Valentin Gill has been most coöperative and painstaking in preparing the photographic material. Miss Hazel Connell, Supervisor of the Central Record File in the Bureau of Tuberculosis, has rendered valuable aid in the collection of the record material for the study.

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# FUNCTIONAL PULMONARY CAPACITY AND SURGICAL RISK<sup>1</sup>

Correlation between Clinical Estimation and Functional Studies

LOUIS LEVY, II, JOHN H. SEABURY AND EDGAR HULL

The purpose of the present study was to determine whether the authors could properly appraise the percentage distribution of respiratory and ventilatory function between the two lungs, having knowledge of the complete clinical picture, radiological data and vital capacity determinations, without the use of bronchspirometric studies.

The proper equipping and maintenance of a station for the evaluation of pulmonary function requires a significant amount of money. In addition, when such evaluation is concerned principally with the tuberculous, factors of risk to patient and personnel must be considered. The present study arose out of an awareness of these factors together with considerable curiosity as to how accurately pulmonary function might be evaluated clinically by those whose work is concerned not only with the clinical care of the tuberculous but also with the laboratory determination of the ventilatory and respiratory capacity. The value of a station for the study of pulmonary function in relation to investigation of cardiopulmonary physiology is undoubted, but how much clinical information which cannot be obtained by simpler and less expensive means is supplied by such a station?

## PROCEDURE

The Lung-Station records of all patients studied during the past two and one-half years were reviewed to determine which ones had undergone successful bronchspirometry with the accumulation of reliable data. Sixty-three such records were selected and the hospital accession numbers recorded. Four months later the hospital records of these patients were analyzed. All possibly pertinent data from the recorded history and physical examination were summarized for each patient. The results of all special procedures, such as bronchoscopy, were listed together with the laboratory findings and vital capacity determinations. Fluoroscopic examination had been done on all but 3 patients. However, this examination was not carried out by any one of us and we were dependent upon the information contained in the records. Careful fluoroscopy with particular attention to the extent and type of diaphragmatic motion had not been a routine practice of the Lung Station during this study. It has been the policy of the Lung Station to require that a bronchoscopy be done on each patient with tuberculosis prior to bronchspirometric study. There have been a few exceptions to this rule. The reports from the Lung Station were withheld. Special effort was directed toward securing a past history of pneumonia, pleurisy or other cardiorespiratory disease. The three authors then reviewed each summary at the time serial chest roentgenograms were shown (up to the last X-ray film preceding Lung-Station study). Each case was then discussed and, with the roentgenograms still in view, a clinical estimate was made of the percentage distribution of pulmonary function between the two lungs, both as to ventilatory and respiratory function. A decision was agreed upon in regard to the patient's ability to

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withstand the surgical procedure which was contemplated at the time the patient was referred to the Lung Station. It was surprisingly easy to secure agreement on both questions following such review of each patient.

After all 63 patients had been reviewed, the tabulated Lung-Station data and the conclusions derived therefrom were compared with the clinical evaluation. Where significant discrepancy existed, both sets of data were again reviewed with the X-ray films in an effort to explain the discrepancy.

Pulmonary function studies included determination of the total pulmonary capacity and its subdivisions, the maximum breathing capacity, breathing reserve, minute ventilation and oxygen consumption per minute. From these data were calculated the ratio of residual to total pulmonary volume, the ratio of breathing reserve to maximum breathing capacity (dyspnea level) and the ventilatory equivalent (the amount of air in liters which must be ventilated in order to absorb 100 ml. of oxygen). A modification of the Benedict-Roth respirometer was employed for determinations of the pulmonary volumina. The maximum breathing capacity was determined by having the patient breathe outside air and, utilizing flutter valves, collecting the expired air in a Tissot spirometer. The residual air was ascertained by means of the open circuit method described by Cournand *et al.* (1).

The degree of emphysema was estimated, as suggested by Cournand *et al.* (2), from the retardation and prolongation of expiration, inability to return to the initial expiratory level on successive deep breaths and alterations in the maximum breathing capacity. The percentage of nitrogen in the expired air after seven minutes of breathing oxygen also gave information concerning the degree of emphysema.

Bronchspirometric determinations were performed on all patients, utilizing the Zavod catheter for bronchial intubation. The technique of intubation was similar to that described by Zavod (3). It is noted occasionally that a patient will have paroxysms of coughing after placing the catheter tip in the left main stem bronchus. This is due to an insufficient amount of the anesthetic agent being in contact with the mucous membrane at this point. For such occurrences it has been our recent practice to pass a radiopaque ureteral catheter down one or both channels of the Zavod catheter and introduce one or 2 ml. of 4 per cent cocaine.

The percentage distribution of respiratory and ventilatory function between the two lungs was calculated from the bronchspirometric data. Absolute figures for respiratory and ventilatory function derived from bronchspirometric determinations are not valid, but the percentage distribution of function between the two lungs can be demonstrated quite accurately.

In addition to the ventilatory equivalent of oxygen for the two lungs, a new determination, the efficiency quotient, was introduced by one of us (J. H. S.). The *efficiency quotient* is calculated by dividing the percentage of total oxygen absorbed by each lung by the percentage of the total ventilation of each lung. For example, if the right lung absorbs 80 per cent of the total oxygen, while being responsible for 40 per cent of the total ventilation, its efficiency quotient (E. Q.) would be 2.0. This figure tells how efficient the two lungs are in relation to each other. The higher the figure for E. Q., the more efficient a lung is in comparison with the other lung. The figure for the E. Q. does not represent an absolute figure for oxygen consumption or ventilation; it is only an expression of the efficiency of each lung in relation to the combined function of the two lungs, taking into consideration how much of the total ventilation each lung utilizes to absorb its percentage of the total oxygen absorption. The E. Q. gives no indication of the absolute figures for total pulmonary function or the function of each lung. It merely expresses the efficiency of each lung in comparison to the total pulmonary function, regardless of

whether the absolute figures for respiratory and ventilatory function are within normal limits or not.

### RESULTS

Sixty-three bronchspirometric determinations were considered satisfactory for analysis. In table 1 are listed the clinical estimations and bronchospiro-

TABLE 1

*A comparison of clinical estimates and functional respiratory tests in 15 patients in whom marked discrepancy existed between the two sets of data*

Pt.	V.C.	M.B.C.	M.O.C.	L.S. % V. R	EST. % V. R	L.S. % V. L	EST. % V. L	ER- ROR	L.S. % O. R	EST. % O. R	L.S. % O. L	EST. % O. L	ER- ROR	V.E. R	V.E. L	E.Q. R	E.Q. L
13	2.29	87.6	0.246	66.7	50	33.3	50	16.7	77.8	40	22.2	60	37.8	2.2	3.9	1.17	0.67
19	—	—	—	29.9	10	70.1	90	19.9	36.4	10	63.6	90	26.4	1.4	1.8	1.22	0.91
21	3.06	83.4	0.203	60.6	40	39.4	60	20.6	37.1	30	62.9	70	7.1	2.4	0.92	0.61	1.60
27	2.26	70.2	0.214	50	10	50	90	40	26.7	10	73.3	90	16.7	3.0	1.1	0.53	1.47
31(a)	1.88	68.9	0.299	68.8	40	31.2	60	28.8	52.4	35	47.6	65	17.4	1.9	0.93	0.76	1.52
31(b)	1.88	81.2	0.121	63.6	40	34.4	60	23.6	71.4	35	28.6	65	36.4	1.5	1.04	1.12	0.83
34	2.74	100	0.263	41.4	30	58.6	70	11.4	53.3	20	46.7	80	33.3	2.6	3.2	1.13	0.92
36	1.50	75.9	0.324	70.6	30	29.4	70	40.6	46.7	20	53.3	80	26.7	4.6	1.6	0.66	1.81
38	2.07	73	0.157	57.2	25	42.8	75	32.2	42	20	58.0	80	22	3.4	2.3	0.73	1.36
43	1.7	37.9	0.246	76.2	50	23.8	50	26.2	78.6	50	21.4	50	38.6	2.3	2.7	1.03	0.90
45	2.24	95.1	0.278	—	30	100	70	30	—	100	20	80	20	—	1.9	—	1.0
54	2.05	90.6	0.150	83.3	70	16.7	30	13.3	97	70	—	3	27	1.8	—	1.2	—
59	3.63	115	0.292	64	35	36	65	29	58.1	40	41.9	60	18.1	3.4	2.7	0.90	1.16
60	2.69	87.6	0.306	56.4	20	43.6	80	36.4	33.3	20	66.7	80	13.3	3.6	1.4	0.59	1.53
61	1.41	32.5	0.235	50	80	50	20	30	75	65	25	35	10	1.5	4.4	1.5	0.5
63	2.5	66	0.235	47	90	53	10	43	63	85	37	15	22	2.0	1.07	1.3	0.70

Pt.—Patient.

V.C.—Vital capacity in liters.

M.B.C.—Maximum minute breathing capacity in liters.

M.O.C.—Minute oxygen consumption in liters.

L.S.—Lung Station.

Est.—Estimated clinically.

% V.—Percentage ventilation.

% O.—Percentage oxygen consumption.

R—Right lung.

L—Left lung.

V.E.—Ventilatory equivalent.

E.Q.—Efficiency quotient.

(a)—First study.

(b)—Second study.

metric calculations of pulmonary function for each lung in those patients in whom a considerable discrepancy existed. The discrepancy between bronchspirometric and clinical estimation of ventilatory and respiratory function was calculated in absolute figures, not in percentage of error. This difference, when applied to either ventilatory or respiratory function, was greater than

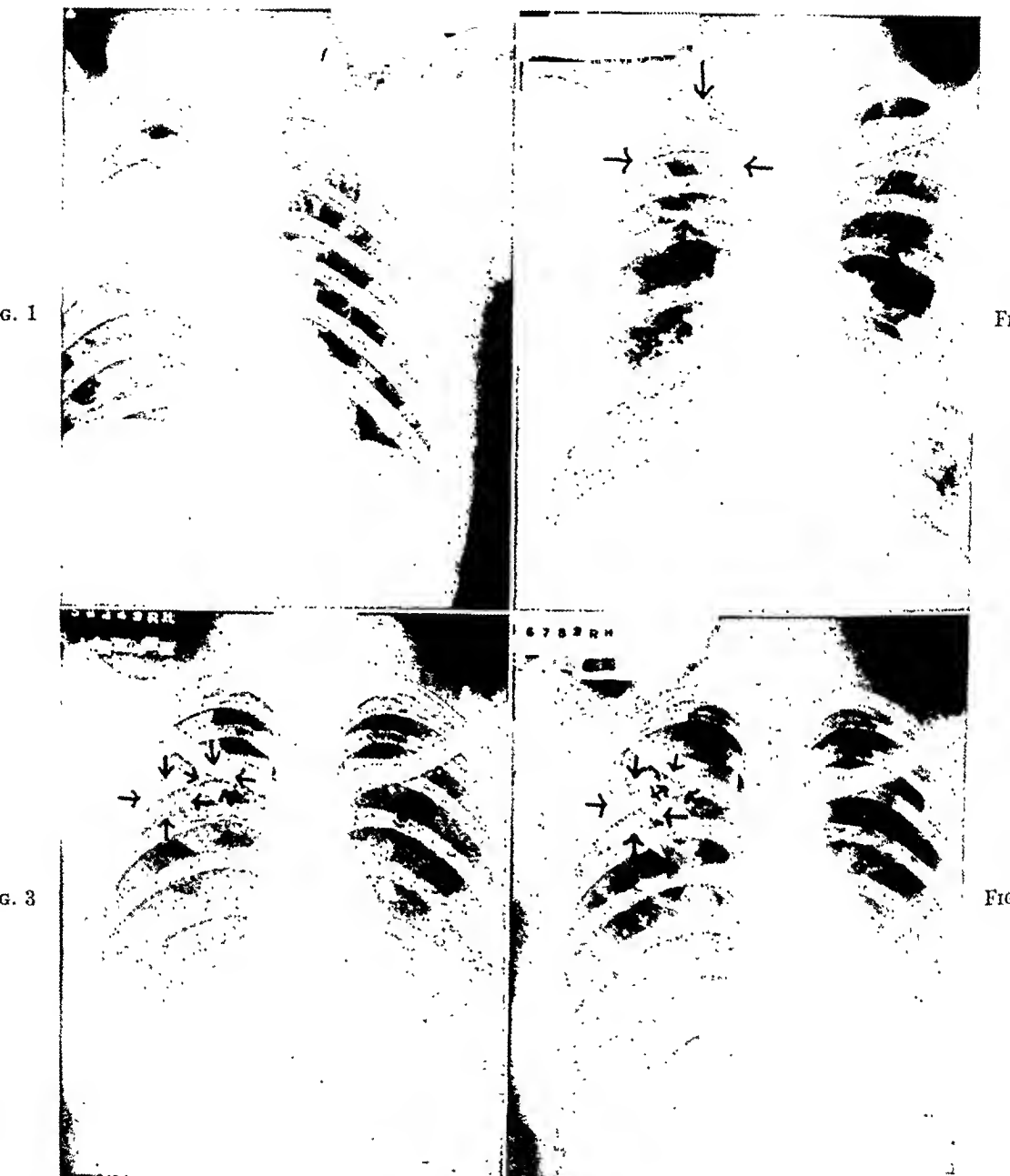
15 per cent in 31 cases, over 20 per cent in 24 cases, over 25 per cent in 15 cases and exceeded 30 per cent in 8 cases. It should be noted that clinical judgment in regard to the ability of each lung to absorb oxygen was in error *by absolute figures* of more than 15 per cent in 21 cases, 20 per cent in 12 cases, 25 per cent in 7 cases and 30 per cent in 3 cases. Clinical judgment failed to estimate the ventilatory function of each lung by more than 15 per cent in 26 cases, 20 per cent in 17 cases, 25 per cent in 10 cases and 30 per cent in 5 cases.

Concerning the advisability of surgery there was a disagreement between the conclusions derived from clinical evaluation and those derived from Lung-Station studies in 6 cases. A thoracoplasty in one patient (no. 47) and a lobectomy in another patient (no. 2) were contraindicated on the basis of Lung-Station studies and were indicated on the basis of clinical evaluation. Operation was not performed on these 2 patients. Phrenemphraxis was contraindicated by Lung-Station determinations and was considered tolerable by clinical estimation of pulmonary function in one case (patient 43). This patient had a phrenic crush performed; however, the operation was unsuccessful, probably due to failure to cut the accessory phrenic roots, and normal diaphragmatic motion was maintained. Thoracoplasty was indicated in one case (patient 32) on the basis of Lung-Station evaluation, but the patient was considered to be a border-line risk by clinical evaluation. No surgical therapy was undertaken in this case. Thoracoplasty was contraindicated in one patient (no. 65) and considered a border-line risk in another patient (no. 4) following Lung-Station studies. Both these patients were considered to be suitable candidates for thoracoplasty on the basis of clinical evaluation and had a thoracoplasty performed. The patient who was a border-line risk (no. 4) became markedly dyspneic following his second-stage thoracoplasty and, after twelve hours of severe respiratory embarrassment and paradoxical respiration, he lapsed into irreversible shock and died. The other patient (no. 65) became extremely dyspneic, requiring continuous oxygen therapy, following her first-stage thoracoplasty and appears to be pursuing a downhill course.

#### DISCUSSION

When clinical evaluation of pulmonary function was made, we took into consideration the effects of pleurisy, parenchymal disease, phrenic paralysis and various other factors affecting pulmonary function which have been emphasized by others (4, 5, 6, 7, 8, 9, 10). The marked diminution in ventilatory and consequently respiratory function resulting from diaphragmatic paralysis, the possibility of contralateral compensatory mechanisms following collapse therapy, the relatively minor effect of parenchymal disease and the relatively major effect of pleural involvement and the variability in limitation of function imposed by reëxpansion of a collapsed lung were taken into consideration in clinical evaluation. Inability to induce a pneumothorax on repeated attempts was considered as evidence of at least localized pleural symphysis. X-ray films were examined for evidence of pleuritis, adhesions of all types, mediastinal shift or fixation, areas of emphysema and other radiological findings which





FIGS. 1-4

FIG. 1. Patient 19 in table 1.

	<i>Lung Station Results</i>	<i>Clinical Estimation</i>
Percentage ventilation, right.....	29.9	10.0
Percentage ventilation, left.....	70.1	90.0
Percentage oxygen consumption, right.....	36.4	10.0
Percentage oxygen consumption, left.....	63.6	90.0

would help in the clinical evaluation of a patient's respiratory and ventilatory function. Complete historical and laboratory data, exclusive of Lung-Station studies but including vital capacity determinations, were carefully considered in the light of the factors mentioned above. As can readily be seen from the data in table 1, many discrepancies existed between estimation of respiratory and ventilatory function by clinical evaluation and by Lung-Station studies. Those cases in which a large error occurred were reëvaluated. Some of these cases will be discussed in order to demonstrate the sources of our errors in estimation of pulmonary function by clinical evaluation alone.

### CASE REPORTS

Three weeks prior to Lung-Station studies, *patient 19* (figure 1) had undergone an exploratory thoracostomy, at which time three inches of the third right rib had been removed and a tube placed in the lung. At the time of operation no free pleural space was found. Because we believed there was evidence of more than localized pleuritis by X-ray and because we knew the surgical findings of pleural symphysis, we estimated about 90 per cent of the ventilatory and respiratory function was supported by the left side. During reëvaluation of this patient, close inspection of the chest X-ray film revealed a poorly outlined, but definitely present pneumothorax over the lower one-third and apex of the right lung. This represented the only error of observation which we were able to detect. The error might have been avoided if the operative note, showing no pleural space, had not been known to us.

*Patient 21* (figure 2) had a history of pleurisy on the right for four months prior to the institution of a right pneumothorax which was complicated by numerous adhesions.

FIG. 2. Patient 21 in table 1.

	<i>Lung Station Results</i>	<i>Clinical Estimation</i>
Percentage ventilation, right.....	60.6	40.0
Percentage ventilation, left.....	39.4	60.0
Percentage oxygen consumption, right.....	37.1	30.0
Percentage oxygen consumption, left.....	62.9	70.0

FIG. 3. Patient 31 in table 1. (a) Study prior to reinstitution of right pneumothorax.

	<i>Lung Station Results</i>	<i>Clinical Estimation</i>
Percentage ventilation, right.....	68.8	40.0
Percentage ventilation, left.....	31.2	60.0
Percentage oxygen consumption, right.....	52.4	35.0
Percentage oxygen consumption, left.....	47.6	65.0

FIG. 4. Patient 31 in table 1. (b) Study following reinstitution of right pneumothorax. Note atelectasis at left base.

	<i>Lung Station Results</i>	<i>Clinical Estimation</i>
Percentage ventilation, right.....	63.6	40.0
Percentage ventilation, left.....	34.4	60.0
Percentage oxygen consumption, right.....	71.4	35.0
Percentage oxygen consumption, left.....	28.6	65.0

The right lung was reexpanded six months after pneumothorax had been started. One year following reexpansion, he was studied in the Lung Station. The history of a right-sided pleurisy and the reexpansion of the lung on that side led us to believe that pleural symphysis probably existed despite the absence of X-ray evidence suggesting pleuritis. This resulted in an underestimation of ventilatory function on the right side which, as seen from the bronchspirometric tracings, was about 60 percent of the total ventilatory function. Pleurisy and the abandonment of a pneumothorax in this patient had not affected his ventilatory function on the right side. It is interesting to note in this case that the large cavity in the right apex probably accounts for the normal percentage distribution of ventilatory function with the markedly decreased respiratory function on this side. This factor had been considered on his first evaluation.

*Patient S1* (figures 3 and 4) had a right pneumothorax induced and abandoned prior to admission to the Charity Hospital. It was discontinued at once due to adhesions and was not present at the time of the Lung-Station studies. We had estimated that the ventilatory and respiratory function had been diminished by what appeared to be pleuritis over the superior one-third of the lateral portion of the right lung in addition to the presence of cavitation. As will be seen from figure 4, the pleuritis only involved the area around the cavity and probably had only a slight effect in limiting pulmonary function. In addition, it will be noted in figure 3 that the left diaphragm is flat in its medial three-fourths, suggesting a diaphragmatic pleuritis with a consequent reduction in function of the left lung. Following our first study of this patient, a right pneumothorax was reestablished and, after this, she was studied again in the Lung Station (figure 4). It will be seen from table 1 that both respiratory and ventilatory function on the right side were underestimated by clinical evaluation. This shows that this lung which had been partially collapsed and was adherent in several areas to the chest wall still maintained a moderate amount of ventilatory function. The effect of mediastinal shift and compression of the contralateral lung, although considered, may have been underestimated. The intrapleural pressure on the right was positive. The percentage figures for ventilation on the right and left remained approximately the same since the reduction in ventilatory function on the right due to the presence of a pneumothorax with adhesions was partially compensated for by a reduction of ventilatory function on the left due to its compression by the mediastinal shift. The decrease in percentage of oxygen absorption on the left was probably due to a combination of factors including atelectasis with mediastinal shift and retained secretion in the bronchioles.

*Patient S4* (figure 5) had a right-sided hydrothorax following a pneumothorax at the time pulmonary function studies were carried out. The presence of fluid on the right side did not reduce pulmonary function as much as we had estimated it would. There is no evidence of mediastinal shift in this X-ray film. Either the mediastinum was fixed or it was not under pressure.

*Patient S8* (figure 6) had a right pneumothorax maintained for six months which was then abandoned. One year later attempts were made to reestablish the right pneumothorax. When these efforts failed, the patient was referred to the Lung Station for study. The clinical opinion that pulmonary function on the right was seriously limited was based on the evidence of pleural symphysis, cavitation and parenchymal infiltration on this side. The finding of only slight reduction of pulmonary function on the right according to bronchspirometry cannot be definitely explained. Since bronchspirometry is a relative

determination, unrecognized pleural symphysis on the left could easily reduce the function on this side so that by comparison the right would appear to be nearly normal. If this were the correct explanation, total pulmonary function would be more severely restricted than the record of this patient demonstrates. A more likely explanation would be that there was predominantly parenchymal disease on the right without significant pleural symphysis despite the evidence to the contrary. This is supported by the normal distribution of ventilatory function and the definite impairment of oxygen absorption on the right. There remains the possibility that pleural symphysis may not always produce serious limitation of pulmonary function, although previously published evidence is to the contrary.

*Patient 59* (figure 7) was given a right pneumothorax which was complicated by a hydrothorax four years prior to Lung-Station studies. On the basis of the history and the radiological findings of mediastinal shift to the right and diaphragmatic pleuritis, we estimated that there would be a moderate reduction of pulmonary function on the right. Lung-Station studies revealed no limitation of function on the right. There may again have been unrecognized pleuritis on the left or little limitation of function resulting from the pleuritis on the right side.

*Patient 61* (figure 8) exhibited X-ray evidence of pleuritis on the left side. This led us to overestimate the diminution in ventilatory function on that side by 30 per cent. Bronchospirometric tracings showed an equal distribution of ventilatory function between the two sides.

Following the induction of right pneumothorax, *patient 60* (figure 9) developed a complicating pleural effusion. Oleothorax was then substituted and maintained for one year. The gomenol and paraffin oil were then removed from the right pleural space and left pneumothorax attempted. No free pleural space was found on the left. Four years later this patient was referred to the Lung Station for study. This history, together with the prominent changes on the right seen on X-ray films, led us to estimate that severe limitation of function was present on the right. Bronchospirometric studies revealed a normal distribution of ventilatory function but poor oxygen consumption ( $E. Q. 0.59$ ) on the right. In this case we were led into error by the abundant historical and X-ray evidence of pleural disease on the right and the normal radiological appearance on the left. The history of failure to induce left pneumothorax should have been considered more seriously. The impairment of oxygen consumption on the right is probably due to the extensive fibrocalcareous parenchymal disease with apical cavitation.

The cases just discussed, together with similar instances of significant disagreement between actual determination of the distribution of pulmonary function between the two lungs and clinical opinion of its distribution, are listed in table 1. After consideration of this table, we are forced to the conclusion that our combined clinical judgment is not sufficiently accurate to determine which patients may be advised to undergo surgery *when clinical observations indicate that the margin of safety is not of considerable width*. Without bronchospirometric studies one cannot properly appraise the percentage distribution of pulmonary function even when the complete clinical picture, radiological data and vital capacity determinations are taken into consideration.

FIG. 5



FIG. 6



FIG. 7



FIG. 8



FIG. 9



Information, not otherwise obtainable, is gained with sufficient frequency to justify the expense, time and risks entailed.

Although there is abundant evidence that a certain amount of risk to the patient is an integral part of bronchspirometry, we feel that this risk need not be excessive. We require, with few exceptions, that each patient undergo bronchoscopic examination prior to bronchspirometry in order to detect endobronchial disease. If endobronchial tuberculosis, bronchial stenosis, or abnormal mucosal bleeding is encountered, we consider it a definite contra-indication to bronchspirometry. We will not do bronchspirometry on patients who have had frank hemoptysis or blood-streaked sputum during the week preceding the scheduled study. If the patient is febrile we postpone bronchspirometric examination unless there is some special reason for having

FIG. 5. Patient 34 in table 1.

	<i>Lung Station Results</i>	<i>Clinical Estimation</i>
Percentage ventilation, right.....	41.4	30.0
Percentage ventilation, left.....	58.6	70.0
Percentage oxygen consumption, right.....	53.3	20.0
Percentage oxygen consumption, left.....	46.7	80.0

FIG. 6. Patient 38 in table 1.

	<i>Lung Station Results</i>	<i>Clinical Estimation</i>
Percentage ventilation, right.....	57.2	25.0
Percentage ventilation, left.....	42.8	75.0
Percentage oxygen consumption, right.....	42.0	20.0
Percentage oxygen consumption, left.....	58.0	80.0

FIG. 7. Patient 59 in table 1.

	<i>Lung Station Results</i>	<i>Clinical Estimation</i>
Percentage ventilation, right.....	64.0	35.0
Percentage ventilation, left.....	36.0	65.0
Percentage oxygen consumption, right.....	58.1	40.0
Percentage oxygen consumption, left.....	41.9	60.0

FIG. 8. Patient 61 in table 1.

	<i>Lung Station Results</i>	<i>Clinical Estimation</i>
Percentage ventilation, right.....	50.0	80.0
Percentage ventilation, left.....	50.0	20.0
Percentage oxygen consumption, right.....	75.0	65.0
Percentage oxygen consumption, left.....	25.0	35.0

FIG. 9. Patient 60 in table 1.

	<i>Lung Station Results</i>	<i>Clinical Estimation</i>
Percentage ventilation, right.....	56.4	20.0
Percentage ventilation, left.....	43.6	80.0
Percentage oxygen consumption, right.....	33.3	20.0
Percentage oxygen consumption, left.....	66.7	80.0

it done at that particular time. While observing the stated precautions, we have had several instances of recurrent bleeding following bronchspirometry in patients who had had recent hemoptysis. Brief febrile episodes frequently occurred following bronchial catheterization. To date only one patient has been known to have post-bronchspirometric spread of tuberculosis of a degree sufficient to be detected by X-ray. We have seen 2 reactions to cocaine and 2 to pontocaine, no one of which was serious.

#### SUMMARY

1. Sixty patients with pulmonary tuberculosis and 3 with lung abscess form the basis of the present study.

2. A clinical evaluation of the percentage distribution of respiratory and ventilatory function between the two lungs was made in each case. History, physical examination, radiological and laboratory findings, including bronchoscopic examination and vital capacity determinations, were considered in the clinical evaluation. Factors affecting pulmonary function, which have been stressed by others, were taken into consideration when a clinical evaluation was made.

3. Lung-Station studies included total pulmonary function and bronchspirometric determinations of individual lung function.

4. Significant discrepancy between clinical evaluation and bronchspirometric determinations of percentage distribution of pulmonary function between the two lungs was a frequent occurrence.

5. Clinical judgment failed to estimate the partition of ventilation or of oxygen consumption, or both, between the two lungs by the following percentages *in absolute figures* (not percentage of error): over 15 per cent in 34 cases, over 20 per cent in 24 cases, over 25 per cent in 15 cases and more than 30 per cent in 8 cases. Errors of such magnitude can be of grave importance to patients whose acceptance for thoracic surgery has been largely on the basis of a "just acceptable" vital capacity and little evidence of disease in the hemithorax opposite to the one on which surgery is proposed.

6. Reëvaluation of these cases brought to light a few of the sources of error in clinical evaluation. Cases demonstrating these points are discussed.

7. The value of Lung-Station studies in evaluating the percentage distribution of pulmonary function and the surgical risk involved is again emphasized by our findings.

#### SUMARIO

##### *La Capacidad Pulmonar Funcional y el Riesgo Quirúrgico*

1. Base para el estudio actual la ofrecen 60 enfermos con tuberculosis pulmonar y 3 con absceso pulmonar.

2. En cada caso hízose una justipreciación clínica de la distribución porcentual de la función respiratoria y la ventiladora entre los dos pulmones. En la justipreciación consideráronse la historia, examen físico, hallazgos radiológicos

y de laboratorio, incluso el examen broncoscópico y las determinaciones de la capacidad vital. También se tomaron en cuenta los factores que afectan la función pulmonar y que otros han recalado.

3. Los estudios realizados comprendieron la función pulmonar total y las determinaciones broncoespirométricas de la función de cada pulmón.

4. Con frecuencia se encontraron discrepancias significativas entre la justipreciación clínica y las determinaciones broncoespirométricas de la distribución porcentaria de la función pulmonar entre los dos pulmones.

5. El criterio clínico fracasó en el cálculo del reparto, entre los dos pulmones, de la ventilación o del consumo de oxígeno, o de ambos, en los siguientes porcentajes en cifras absolutas (no porcentaje de error): más de 15 por ciento en 34 casos, más de 20 por ciento en 24 casos, más de 25 por ciento en 15 casos y más de 30 por ciento en 8 casos. Errores de tal magnitud pueden revestir suma importancia tratándose de enfermos cuya aceptación para la cirugía torácica ha sido en gran parte a base de capacidad vital "apenas aceptable" y pocos signos de enfermedad en el hemitórax opuesto al propuesto para intervención.

6. La revaluación de esos casos puso de manifiesto algunas de las causas de error en la justipreciación clínica. Preséntanse casos que ilustran estos puntos.

7. Estos hallazgos recalcan de nuevo el valor de los estudios realizados en la Estación Pulmonar para apreciar la distribución porcentaria de la función pulmonar y el riesgo quirúrgico corrido.

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# ARTERIOVENOUS FISTULA OF THE LUNG<sup>1,2</sup>

## Its Hereditary and Clinical Aspects

ALFRED GOLDMAN

Arteriovenous fistula of the lung producing secondary polycythemia, cyanosis and clubbing was discovered in each of two brothers. The first of these cases was reported in 1943 (1) as a cavernous hemangioma of the lung, a term which is synonymous with arteriovenous fistula or arteriovenous aneurysm. Since the report, the patient had a pneumonectomy with complete disappearance of his symptoms and signs. A recent examination of his brother showed him to have a very similar lung lesion with the same clinical picture. The disease is a congenital inherited anomaly and is much more frequent than originally thought. Some of the cases are part of the syndrome known as hereditary hemorrhagic telangiectasia, a well known and relatively common inherited vascular disease. Others have only the lung lesion without any other evidence of multiple telangiectases, though it is still probable that the fistula is a manifestation of hereditary telangiectasia. A complete review of the literature is given. The clinical-pathological picture based on all the known cases is described.

A description of the 2 cases follows.

### CASE REPORTS

*Case 1: (E. L.)* This was a 22-year-old male who had been cyanotic since infancy and had an unexplained shadow in his lung since the age of 6. Dyspnea and cyanosis were prominent since he was 15. He was treated ineffectively for several years as a case of polycythemia vera. His chief complaints were headaches, dyspnea and thickness of speech. Examination on June 20, 1942 showed him to be definitely cyanotic with marked clubbing of his hands and feet. He had a small hemangioma on his left upper lid. His heart and lungs were negative. Blood pressure was 110/80. Repeated blood counts showed a range from 7,000,000 to 11,450,000 red cells. Hemoglobin ranged from 137 to 180 per cent. Blood volume was 8,170 cc.; plasma volume 2,450 cc.; cell volume 5,720 cc. Arterial oxygen capacity was 28.4 vol. per cent; arterial oxygen content 19.9 vol. per cent; arterial oxygen saturation 70 vol. per cent. Venous pressure was 115 mm. of water in recumbent position. Decholin circulation time was twelve seconds arm to tongue. Ether circulation time was nine seconds arm to lung. During the ether test, the patient had severe transitory needle-like pain throughout the entire body which lasted fifteen seconds. Electrocardiogram showed right ventricular preponderance. An X-ray film of his chest showed an irregular shadow in the left mid-lung field, which extended laterally from the hilum to the periphery of the lung. Several small spherical shadows were noted near the hilum. The entire mass could be seen to pulsate on fluoroscopy and kymography (figures 1, 2, 3). A diagnosis of cavernous hemangioma of the lung, acting as an arteriovenous fistula, was made on the basis of the long-standing pulsat-

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<sup>2</sup> Presented before the Medical Section at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 18, 1947.

ing lung lesion, the oxygen unsaturation of arterial blood, the polycythemia, clubbing and absence of disabling heart disease. Operation was advised. The patient returned for operation on October 29, 1945. The only new finding was the presence of a violently pulsating vessel along the left fifth intercostal space, which arose from the left axilla. Prior to operation, his red count was 7,900,000; hemoglobin 173 per cent; white count 4,500; actual packed red cells 79 per cent; platelets 2,370,000; reticulocytes 0.70 per cent. On November 1, 1945, a left pneumonectomy was performed by Dr. Evarts Graham.

*Operative notes:* "The tissues were very vascular and large intercostal vessels were encountered which bled severely. The lung was adherent to the chest wall. The adhesions were very vascular. The pulmonary artery at the hilum was bulbous, as was the pulmonary vein lying just inferior to the artery."

*Pathologic specimen:* (Report by Dr. N. A. Womack) "The left lung showed normal fissure formation, but the upper lobe was relatively much larger at the expense of the lower lobe. It was cyanotic and on pressure did not possess the normal resiliency usually encountered. Both the pulmonary artery and vein were much larger in diameter at the point of section, and the wall of each was thickened and irregular. Inspection into the lumen of the pulmonary artery showed large openings in its primary branches. When fluid was injected into the pulmonary vein, it promptly appeared in these arterial openings without obviously going through a capillary bed. The picture was one of diffuse arteriovenous communications throughout both the upper and lower lobes. Because of the obvious microscopic picture and the value of demonstrating the size of these communications, it was felt worth while to forego microscopic study in order to have an adequate cast of the lung. Accordingly, liquid latex was injected into the pulmonary vessels, the latex was allowed to harden and the lung tissue was digested by placing it in sulphuric acid. Examination of the cast (figure 4) shows many large communications between the pulmonary artery and vein, beginning high up in their origin and not involving the smaller branches quite so noticeably. Both artery and vein are 4 cm. in diameter at their greatest portion. There are numerous nodular dilatations noted, particularly in the vein, although as a whole one is impressed by the fact that the artery presents almost the same picture as does the vein. While it is slightly smaller in diameter, the ramifications and the tortuosities are almost identical, thus differing in considerable extent from the pictures seen in arteriovenous communications in the general circulatory system. Because of the position and number of these communications, they obviously represent developmental anomalies and are not traumatic in origin. While such a lesion could be considered in its early formation phase as an angioma, in the present picture this is obviously not a tumor in any neoplastic sense. The malformation as described can best be explained by hydraulic law. The diagnosis is congenital malformation of lung, arteriovenous fistula."

Immediately after the operation, the patient's color improved. On November 2, 1945, his red count was 5,410,000; hemoglobin 122 per cent; white count 14,200 and platelets 308,370. Four days later, his cyanosis had disappeared. His red count and hemoglobin continued to drop and on November 5, 1945 his red count was 4,830,000; hemoglobin 100 per cent; white count 9,400; platelets 621,000 and reticulocytes 1.8 per cent. On November 6, 1945, arterial oxygen content was 18.5 vol. per cent; arterial oxygen capacity 18.5 vol. per cent and arterial oxygen saturation 100 vol. per cent. Blood pressure was 104/78. The only postoperative reaction was an attack of auricular fibrillation which lasted two days and disappeared coincident with the use of Cedilanid and aspiration of his left chest. On November 8, 1945, his electrocardiogram showed a normal curve. The patient was last examined on September 16, 1946. He felt very well, had



FIGS. 1-5

lost his cyanosis and dyspnea and his clubbing had almost completely disappeared. His red count was 4,770,000; white count 6,200; hemoglobin 88 per cent and hematocrit reading 45 per cent. An X-ray film of his chest (figure 5) showed a satisfactory operative result.

*Case 2:* (W. L.) The second case is that of the 32-year-old brother who was first seen on September 16, 1946. He gave a history of having had a slightly purplish color for the past six years. He had never indulged in arduous exercise because of dyspnea, although he was able to work steadily as a salesman and had never been incapacitated. His chief complaint was frequent sore throats.

His blood pressure was 120/75. There was a definite cyanosis of the lips and nail beds and slight clubbing of the fingers and toes. Examination of the heart was negative. There was a late blowing systolic murmur, 5 cm. to the left of the upper sternum. His red count was 7,000,000; white count 10,850; hemoglobin 141 per cent; hematocrit reading 64 per cent; arterial oxygen saturation 88.7 vol. per cent. An X-ray film of his chest showed a shadow in the left upper lung field extending out from the hilum to the lateral chest wall, which definitely pulsed on fluoroscopic examination (figure 6). Lamino-grams showed this to be a branching tumor-like mass with a separate spherical shadow close to the main lesion. Vascular connection with the hilum was readily visible (figures 7 and 8). Kymogram was indeterminate. A diagnosis of pulmonary arteriovenous fistula was made. At the present time the patient is considering operation.

#### REVIEW OF THE LITERATURE

Pulmonary arteriovenous fistula is a recently discovered lesion. The first report that can be found in the literature is that of Wilkens (2) in 1918. He describes the postmortem findings of a 23-year-old girl who had one fistula in the left lung and two in the right. No mention is made of the blood counts. DeLange and DeVries Robles (3) in 1923 reported the case of an infant, aged two and one-half months, whose lungs at postmortem showed two pulmonary hemangiomas. No blood counts are given. Bowers (4), in 1936, reported a new-born child who died from pulmonary hemorrhage caused by a ruptured pulmonary hemangioma. In 1939, Duvour *et al.* (5) reported a child of 7 who showed a mass in the lung which when removed proved to be an hemangioma. There was no cyanosis, clubbing or increased red cell count. The child died of pneumonia five years later and several visceral hemangiomas were found at postmortem examination. The first case of hemangioma of the lung complicated by secondary polycythemia was reported by Rodes (6) in 1938 in a 25-year-old male. The diagnosis was made postmortem, following death from pulmonary hemorrhage. Smith and Horton (7), in 1939, were the first to make the diagnosis clinically. Their patient was a 47-year-old male who had been blue since

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FIG. 1. (Upper left) Case 1. Shadow in left upper mid-lung field. July 29, 1942.

FIG. 2. (Centre left) Case 1. Anteroposterior laminogram. Note circular shadows. July 29, 1942.

FIG. 3. (Centre right) Case 1. Lateral laminogram. July 30, 1942.

FIG. 4. (Bottom) Case 1. Latex cast of left lung. A: artery. V: vein. F: fistulous connection.

FIG. 5. (Upper right) Case 1. Postoperative roentgenogram. September 16, 1946.



FIGS. 6-8

FIG. 6. (Top) Case 2. Shadow in left upper lobe. September 16, 1946.

FIG. 7. (Lower left) Case 2. Anteroposterior laminogram. Note circular shadow. September 17, 1946.

FIG. 8. (Lower right) Case 2. Lateral laminogram. September 17, 1946.

birth, had marked clubbing of the extremities, polycythemia and a shadow in the right lung over which a bruit could be heard. Hepburn and Dauphinee (8), in 1942, reported the third case of a 23-year-old female who had polycythemia, clubbing, cyanosis, a 70 per cent arterial oxygen saturation and a shadow in the right middle and lower lobes. For the first time a pneumonectomy was performed with disappearance of her cyanosis, polycythemia and clubbing. The fourth case was reported by the author (1) prior to the operation in 1943. Janes (9) reported the next case, in the same year, of a 30-year-old male who had cyanosis but no clubbing or polycythemia and who was cured by local dissection of four lung lesions, two in each lung. Hemorrhage was the immediate cause for operation. The fifth case of pulmonary arteriovenous fistula with secondary polycythemia was that of Adams *et al.* (10), in 1944, who did a successful pneumonectomy on a 24-year-old male with the exact clinical picture present in the other cases. Jones and Thompson (11), in 1944, also did a successful pneumonectomy on a 24-year-old female who presented the unmistakable clinical picture of pulmonary arteriovenous fistula. She made an uneventful recovery with disappearance of her cyanosis, polycythemia and clubbing. Sisson *et al.* (12), in 1943, reported a 45-year-old colored female who had polycythemia, clubbing, cyanosis and a lesion in the left lung over which a to-and-fro murmur could be heard. The patient died shortly after the injection of diodrast. Post-mortem examination showed arteriovenous aneurysms in both lungs. Alexander (13), in 1945, reported a 41-year-old farmer who had polycythemia, cyanosis, clubbing of the fingers and a shadow in the left base over which a loud systolic murmur could be heard. The patient was thought to have polycythemia vera. He died of a coronary thrombosis and autopsy showed multiple pulmonary hemangiomata. Makler and Zion (14), in 1946, reported a 20-year-old male who had cyanosis, clubbing, polycythemia and several shadows in the lung, over one of which a systolic murmur could be heard. Because of the multiplicity of the lesions, the authors hesitated to advise operation. Lindgren (15), in 1946, reported 3 arteriovenous aneurysms of the lung. He prefers the word aneurysm instead of fistula, as the former suggests a congenital origin to him. His first case was a 30-year-old male who had clubbing, cyanosis, a 90 per cent arterial oxygen saturation, a systolic murmur over the left base and a shadow in the left lung, but no polycythemia. The second case was a 29-year-old male who had cyanosis, polycythemia, clubbing, a systolic murmur over the right anterior lower chest and a shadow in the right base. The lesion was successfully removed by dissection and proved to be multiple arteriovenous aneurysms. The third case was a 25-year-old female who had cyanosis, clubbing, a systolic murmur over the left lower chest in the axillary region, an arterial oxygen saturation of 83.8 per cent, and a shadow in the left lung. The blood counts are not given. Intravenous injection of a radiopaque medium corroborated the diagnosis. The aneurysm was removed at operation along with the lingula of the left lung. The patient's cyanosis quickly disappeared. Bisgard (16) described a 29-year-old white male who had dyspnea, cyanosis, polycythemia, a murmur over the

right lower lobe posteriorly and a pulsating shadow in this region. Lobectomy completely relieved the symptoms and signs. Whitaker (17) reported 2 cases in March, 1947. The first was a female aged 44, who had clubbing, cyanosis, a red count of 6,300,000, hemoglobin 96 per cent and a lesion in the right lower lobe. The patient died following operation. The second case was a 33-year-old male who had a lesion in the left lung over which a harsh murmur could be heard. The patient had no clubbing and the blood counts are not given.

There are now 17 patients with symptom-producing arteriovenous fistulae of the lung in the literature, including the author's second case; 12 were males, 5 were females; 16 were white and one colored. There are 4 case reports of small fistulae or hemangiomas, discovered accidentally at postmortem examination or operation, apparently too small to produce symptoms. Many of the small lesions are naturally missed even at autopsy. A small fistula has no clinical significance, except that it casts a shadow on the roentgenogram and it may be the cause of hemorrhage (4). It is only when the lesion is large enough to produce anoxemia with its accompanying signs and symptoms that the disease becomes clinically important and can be recognized. While the lesion is relatively rare, it is obvious that it has been overlooked in the past, since there were no case reports prior to 1938, and yet 15 were reported in the last five years. As stated in a previous report (1), the symptoms, signs and laboratory findings are so constant that a clinical syndrome due to a pulmonary arteriovenous fistula can be readily established.

*Etiology:* The lesion is a congenital anomaly. Reid (18) states that the embryological explanation for the occurrence of other types of arteriovenous fistula is that the arteries and veins develop out of a common capillary plexus, so that opportunities for persistent connections are always present. The occurrence of the fistula in 2 brothers naturally suggests that the lesion is inherited. Table 1 contains the pedigree of the "L" family. It is assumed that the disease is primarily due to a gene C which may act in a single dose, that is, in Cc persons, or in some cases may have no apparent physical effect on such persons except to make them carriers in a genetic sense. The normal gene is c. Individuals 1 and 2 in the pedigree were probably Cc and cc, it being impossible to state which carried the C gene. Both of them are now dead and neither of them had any of the stigmata of the disease. No. 2, the grandmother of the 2 cases reported, was subject to nosebleeds most of her life. This may be significant as will be shown later. No. 3 died at the age of 46, supposedly of influenza. He had been cyanotic all of his life, had marked clubbing of his extremities and yet was able to carry on his work up to the time of his death. His physician states that he had no evidence of heart disease. It is highly probable that he had a pulmonary arteriovenous lesion. Roentgenograms of Nos. 4 and 5 are negative. No. 6, the father of the 2 cases in this report, has no outward evidence of the lesion. However, a plate of his chest shows definite widening of the right hilar region, strongly suggesting dilated pulmonary vessels. Over the right diaphragm a hemispherical shadow is visible, with the base resting on the diaphragm. This may represent an abnormality of the diaphragm or a vascular mass. It is quite possible

that he has a silent arteriovenous fistula of the lung. An X-ray film of the mother's chest is normal, and there is no record of the disease in the mother's family. No. 6, therefore, is represented as Cc and passed the disease on to his sons even though he is apparently physically well. Nos. 11 and 12 are Cc, having received the C gene from their father and c from the mother. No. 11 is married and has no children. No. 13 died at the age of 9, supposedly of complications following a birth injury. The remaining members of the family are apparently well. According to this explanation of the mode of inheritance, the C gene is said to be a dominant gene with incomplete penetrance, that is, it may act in a single dose (in Cc persons) and produce the disease, or it may be present in the germ plasm without expressing itself in the soma. An individual with the geno-

## PEDIGREE OF L FAMILY

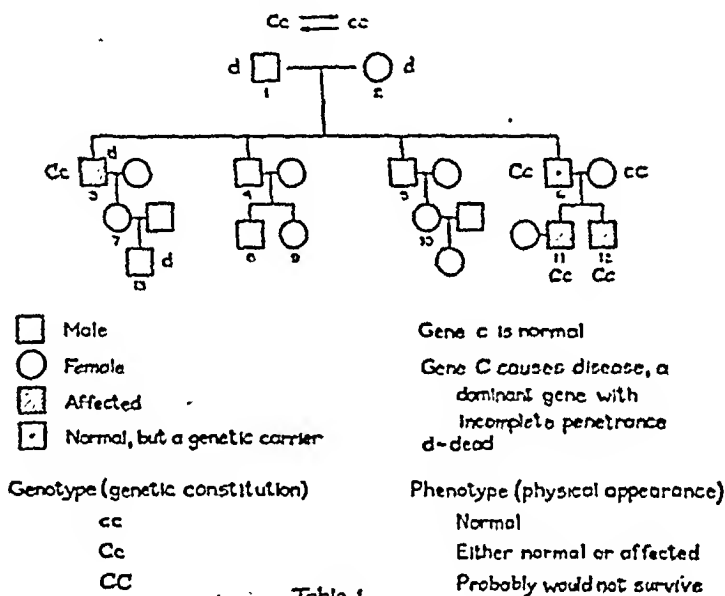


Table 1.

type CC, born of parents each of whom carries the C gene, would presumably not survive. An example of this in a related type of hereditary vascular disease is described by Snyder and Doan (19), who report an 11-weeks-old infant who died of hereditary hemorrhagic telangiectasia with multiple lesions over the entire skin and all internal organs. Both parents had the disease. They consider this as the first recorded instance of a homozygous form of the disease and conclude that the gene for multiple telangiectases is lethal when homozygous.

There is an analogous hereditary disease in chick embryos born of the so-called Creeper stock of fowl, a chondrodystrophic stock (20). Twenty-five per cent of these embryos will have two Creeper factors (homozygous) and the majority of these will die within a few days. The deaths are invariably caused by an arteriovenous fistula, usually between the dorsal aorta and anterior cardinal veins, or



between the vitelline artery and vitelline vein. The result is that the blood is returned to the heart without passing through the yolk-sac capillaries.

*Relation to other hereditary vascular diseases:* In view of the hereditary nature of pulmonary arteriovenous aneurysm, its relationship to other inherited vascular diseases was considered. There are many cases of congenital polycythemia, congenital clubbing and congenital cyanosis in the literature. Most of these reports do not mention study of the lungs, yet many of the cases could very easily fit in with the clinical picture of pulmonary arteriovenous fistula. The most important inherited vascular disease is hereditary hemorrhagic telangiectasia, of which there are over 1,000 cases occurring in one hundred and fifty families. The finding of telangiectases elsewhere in the body in association with hemangioma of the lung would naturally suggest that the pulmonary lesion is another telangiectatic manifestation. This combination is present in about half of the cases of pulmonary arteriovenous fistula. In the other half, no extrapulmonary telangiectases are present.

Multiple telangiectases or so-called Rendu-Osler-Weber's disease is a definite clinical entity, characterized by typical localized dilatations of small vessels to form telangiectases, angiomata or small ruby points with a tendency to bleed. They occur most commonly on the skin of the face and neck and on the buccal and naso-pharyngeal mucous membranes. It is an inherited disease, being transmitted as a simple dominant characteristic. Both sexes are affected and both transmit the disease. Occasionally a generation may be skipped. It is fundamentally a congenital defect of development of the terminal loops of the capillaries with hemorrhage due to fragility of the small vessels. Coagulation time, bleeding time, platelet count and fragility tests are all normal. Epistaxis is the commonest symptom, which usually does not appear before the age of puberty. Telangiectasia may be present in any organ in the body, so that gastro-intestinal bleeding, hemoptysis, hematuria, melena and cerebro-vascular bleeding may take place.

It is obvious that there is considerable difference clinically between the usual case of pulmonary arteriovenous fistula and that of hereditary hemorrhagic telangiectasia. In the former, the chief clinical factor is the anoxemia due to the shunt which in turn causes the polycythemia, cyanosis and clubbing. In the latter, the visible telangiectases and the bleeding from the nose, particularly, are the most striking symptoms. However, overlapping may occur, so that nose-bleeds and telangiectases elsewhere in the body may be present. Usually the symptoms of one form of the disease overshadow the other and this perhaps accounts for the failure in the past to find the lung lesion more frequently. For example, anemia is common in Osler's disease, because of hemorrhage, and this would counteract the finding of polycythemia due to the arteriovenous fistula if present. Case histories culled from the literature exemplify this point and also show how the lung lesions have been overlooked or misdiagnosed. The following case reports are examples in point: (1) Cappon (21), in 1945, cited the case of a 31-year-old woman who had typical multiple telangiectases with epistaxis since

the age of 10. There were four generations in her family with telangiectasia. When she was free of attacks of bleeding, she developed polycythemia with 6,250,000 red cells and 112 per cent hemoglobin. Cappon attributed this to overcompensation. No mention is made of her lungs. The polycythemia suggests the probability of an accompanying arteriovenous fistula. (2) Goldstein (22), 1921, whose name is frequently associated in the literature with multiple telangiectases (Goldstein's heredofamilial angiomatosis), reported a 32-year-old female with a long-standing history of nose bleeds. She had shortness of breath on exertion. There were numerous telangiectases on her back, ears, and nasal septum. She had clubbing of the fingers, marked cyanosis and no evidence of cardiac disease. No blood counts or roentgenogram of the chest are mentioned. There were 11 persons with telangiectases in her family. The case report strongly suggests an arteriovenous fistula of the lung. (3) Rundles (23), in 1943, described a 56-year-old male who had typical hereditary hemorrhagic telangiectasia with lesions on the skin, lips and episodes of nasal and gastrointestinal bleeding. When first seen in 1936, he had a severe anemia. Examination of his chest revealed a continuous murmur in an area localized in the fifth intercostal space below the right nipple. Chest roentgenogram showed a round homogeneous shadow, 4 cm. in diameter, in the right middle lobe, with a prominent vascular trunk to the pulmonary hilum. Fluoroscopy and kymography showed expansile pulsation. Reexamination in 1944 showed the lung lesion as before, possibly slightly larger. There were numerous telangiectases on the lips, tongue, nasal septum and forearms. Gastroscopic examination showed several clusters of telangiectases along the lesser curvature of the stomach and the antrum. Anemia was again noted since there had been recent rectal bleeding. The patient improved on iron therapy and, three months later, he had a red count of 5,700,000 and 109 per cent hemoglobin. Rundles called the lung lesion an aneurysm of the pulmonary artery and states that this is the first time that aneurysm of the pulmonary artery has been described with hereditary hemorrhagic telangiectasia. The lung lesion described in this case is similar in every way to a pulmonary arteriovenous fistula. The subsequent polycythemia following control of the bleeding is highly suggestive. This case, therefore, has definite and important major clinical characteristics of a common type of hereditary hemorrhagic telangiectasia and a symptom-producing pulmonary arteriovenous fistula.

Finally, in studying the family history of other known cases of pulmonary arteriovenous fistula, we get the following facts:

(1) Adams *et al.* (10) report that the father of their case had blue spots on his lips and had been subject to numerous nosebleeds, and he had a shadow in the lungs. Also, other male ancestors in the family were reputed to have nosebleeds and blue spots on their lips.

(2) Lindgren (15) reports a 29-year-old male who had a pulmonary arteriovenous fistula which was successfully removed. About the patient's face were numerous telangiectases. His mother had telangiectases on the face and had

suffered at times from nasal hemorrhages. A brother also had frequent nasal hemorrhages.

(3). Whitaker (17) reports that one of his patients had frequent nosebleeds and that her brother was also subject to epistaxis. The father of his second case had nosebleeds.

(4) The paternal grandmother of the 2 cases reported in this paper had nosebleeds most of her life. There were no other external manifestations.

*Summary of relationship of arteriovenous fistula of the lung to multiple telangiectases:* Pulmonary arteriovenous fistula is a manifestation of hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber's disease, Goldstein's hereditary familial angiomatosis). Reid (18), and Virchow long before him, have stated that angiomata are instances of abnormal arteriovenous communications, no matter what the size and shape of the lesions were. It can be repeatedly shown that: (1) Typical cases of arteriovenous fistula of the lung frequently have telangiectases or hemangiomas in the body, all of which cannot be entirely explained on the basis of the secondary polycythemia. (2) Typical cases of hereditary hemorrhagic telangiectasia may have a symptom-producing arteriovenous fistula of the lung. (3) The children of individuals with multiple telangiectases may have a pulmonary arteriovenous fistula. While one gene is undoubtedly responsible for all the manifestations of multiple telangiectases, it is of interest that, in the family reported here, all of the cases showed primarily only lung lesions. The family tree of all cases of pulmonary arteriovenous fistula should be obtained. All patients with hereditary hemorrhagic telangiectasia should have their lungs carefully studied.

*Pathology:* The specimens obtained at operation and necropsy are all very similar in appearance. The lesion consists of one or more aneurysmal dilations of varying size, usually representing an extension of the pulmonary artery with fistulous connections of varying numbers and sizes to a dilated pulmonary vein. The chief dilatation usually of the vein takes on the appearance of a multilocular sac, ranging up to 7x7x8 cm. (11). Microscopically the wall is lined by endothelial cells. The wall may be thickened, adherent, and it may contain calcified plaques, or it may be thinned out suggesting the possibility of rupture. The lesion is not an hemangioma in the sense of a tumor, but is rather an arteriovenous aneurysm or fistula, congenital in origin. Lesions may be single, or multiple; they may occur in any lobe of the lung and may be present in both lungs of the same patient.

*Symptoms:* Since the disease is congenital, symptoms are apt to start early in life; 8 of the cases had symptoms at birth or early childhood. No case up to the present time has been diagnosed clinically under the age of 20, suggesting that the lesion may become progressive, making the symptoms and signs more manifest with time, and also that the lack of general knowledge of the syndrome causes a delay in diagnosis. As already stated, a small fistula produces no symptoms or signs, and is important only because it is a possible source of hemorrhage, it casts a shadow in the roentgenogram and it is an inheritance factor. The clinical picture is obviously dependent on the amount of blood shunted through the

arteriovenous fistula, that is, the degree of anoxemia produced. Dyspnea is the most common symptom, being present in all cases. Then follows fatigue and weakness, vertigo, faintness, hemoptysis, chest pain, thickness of speech, headache, cough, nosebleeds, convulsions with unconsciousness and temporary paralysis of arm and leg, in the order of their frequency.

*Physical signs:* Cyanosis and clubbing are constant findings in cases of large pulmonary arteriovenous fistula. Hemangiomas or telangiectases elsewhere in the body are present in half of the cases. A murmur described as a systolic or continuous bruit may be heard over the lesion in the majority of the patients; actually in 12 of 17 cases.

The heart is not obviously damaged by the pulmonary arteriovenous fistula, and this fact is used as an important differential point. This is quite in contrast to the finding in peripheral arteriovenous aneurysm, and is explained by the fact that the lesion involves only the pulmonary circulation, the pressure of which is normally low. Study of 15 reports, in which examination of the heart was given, reveals the following: 10 of the cases were said to have normal hearts. In 2 cases (Goldman (1) and Jones (11)) a tendency to right axis deviation was shown on the electrocardiogram without any other evidence of heart disease. In the first of the 2 cases in this report, following pneumonectomy, the electrocardiogram which showed right ventricular preponderance returned to normal. This would suggest that the right heart had been under strain from the effect of the fistula, since pneumonectomy *per se* will not cause a change in the axis (Massie (24)). Venous pressure and circulation time were obtained in a few cases and were normal. Alexander's (13) case, age 41, died of a coronary thrombosis in the anterior left descending branch, and left ventricular hypertrophy was also noted at autopsy. In Sisson's (12) patient, age 45, who died following intravenous diodrast, hypertrophy of the left ventricle, moderate dilatation of the left auricle, moderate hypertrophy of the right ventricle and dilatation of the right auricle with myocardial scarring were found. The authors attribute the congestive failure that this patient had to increased cardiac output due to the arteriovenous fistula. One of Lindgren's (15) patients, age 30, had a typical mitral stenosis, probably on a rheumatic basis. It would seem from a study of the reports that the heart is not affected by the lesion yet, in view of the increased blood volume and the theoretical resistance offered by a large fistula, some cardiac hypertrophy must invariably or eventually take place in a long-standing large shunt. Slight degrees of hypertrophy are difficult to detect. The change in axis deviation to normal following removal of the shunt is suggestive and should be studied in other cases. Most of the fistulae that have been described are in young people, and this may account for the absence of cardiac changes. It is probable, however, that the individual with a large pulmonary arteriovenous fistula who lives long enough will show some cardiac changes attributable to the aneurysm. This should not nullify the importance of so-called "negative cardiac findings" in the differential diagnosis of pulmonary arteriovenous fistula, since any cardiac lesion that will produce cyanosis, clubbing and polycythemia must *per se* be of a very serious and, therefore, easily detectable type.

*Laboratory findings:* Polycythemia was present in every case except the ones reported by Janes (9) and Lindgren (15). In 2 patients (8 and 12) there were previous reports of normal counts, two years and ten years, respectively, before the diagnosis was made, but polycythemia developed later, suggesting that there was a progression of the lesion with an increase in the arteriovenous shunt. Along with the increase in red cells, there is a hyperglobinemia, an increased blood volume and an increased cell mass. The highest red count reported was 11,450,000; the highest hemoglobin 180 per cent (1). The peripheral blood shows no constant changes as occurs in polycythemia vera. The arterial oxygen saturation is always decreased, ranging down to 70 per cent. In spite of the cyanosis, the arterial oxygen capacity and arterial oxygen content are markedly increased, showing an enormous compensatory change. The use of the ether circulation time method for demonstration of veno-arterial shunts, as described by Benenson and Hitzig (25) and suggested by Lansdowne (26), may prove to be of considerable value in diagnosis. In the first case described in this report, the patient had peripheral manifestations of the injected ether, a phenomenon which occurs only in right to left shunts. Lansdowne also suggests that the arm to tongue circulation time may be strikingly decreased.

*Röntgenogram* of the lungs shows a large mass or masses in the pulmonary parenchyma with broad vascular shadows extending to the hilum. Usually one or more spherical shadows can be seen near the large mass; these represent cross-sections of dilated pulmonary vessels. Laminography is helpful in accentuating the vascular shadows. Fluoroscopy and kymography will usually reveal pulsation of the lesions, though this cannot always be demonstrated. Makler and Zion (14) suggest the use of the Valsalva experiment, while the patient is behind the fluoroscopic screen. They state the lesion can be made to decrease and increase while the patient tries to expire with the mouth closed and the nostrils occluded, and then tries to inspire under the same condition. Lindgren (15) makes the same observation. Intravenous diodrast will readily demonstrate the lesion, but in view of the sudden death of the patient following its use by Sisson *et al.* (12) its use should be left in the hands of those properly trained and equipped to use this method. In most cases, the diagnosis can be made without contrast medium. Makler and Zion (14) noted in their patient two additional masses on X-ray examination after a period of three years.

*Differential diagnosis:* The lesion must be differentiated from polycythemia vera, congenital heart disease, emphysema, Ayerza's disease and chronic pulmonary lesions producing polycythemia and clubbing. The combination of a secondary polycythemia, clubbing of the extremities, a lowered arterial oxygen saturation, cyanosis, negative cardiac findings, plus a chronic pulsating intrapulmonary lesion present since birth over which a murmur can usually be heard is pathognomonic of a pulmonary arteriovenous fistula. A family history of multiple telangiectases or the presence of other signs and symptoms of hereditary hemorrhagic telangiectasia would be helpful in a doubtful case. Polycythemia may occasionally be absent. It would be difficult to diagnose a small asymptomatic lesion except by contrast medium.

*Prognosis:* It is doubtful that a patient could have a normal life expectancy with a symptom-producing arteriovenous fistula of the lung. One patient died of a pulmonary hemorrhage at 25, one of coronary thrombosis at 41, one following intravenous injection of diodrast at 45, and one after operation. Danger of hemorrhage is always present, since the walls of the vessels undergo varying degrees of change. The polycythemia, which may be extreme, produces an additional hazard. The heart will ultimately show some changes.

*Treatment:* Pneumothorax is ineffective. Surgery offers the only chance of cure. This may consist of local dissection, lobectomy or pneumonectomy, the type of operation being dependent on the findings at the time of operation. The marked disability of most of the patients, caused by arteriovenous fistula of the lung, makes surgery imperative.

#### CONCLUSIONS

1. The occurrence of arteriovenous fistula of the lung in siblings is reported for the first time.
2. It is a congenital inherited anomaly, occurring in both sexes and transmitted as a dominant with incomplete penetrance.
3. It is a manifestation of hereditary hemorrhagic telangiectasia.
4. A previously reported case diagnosed as a pulmonary arteriovenous fistula was confirmed at operation and cured by pneumonectomy.
5. A new case of arteriovenous fistula of the lung is reported.

#### CONCLUSIONES

##### *Fístula Arteriovenosa del Pulmón*

1. Comunicase por primera vez la ocurrencia de fístula arteriovenosa del pulmón en hermanos.
2. Trátase de una anomalía congénita heredada que afecta a ambos sexos y se transmite como carácter dominante con penetración incompleta.
3. Constituye una manifestación de telangiectasia hemorrágica hereditaria.
4. Un caso previamente comunicado y diagnosticado como fístula arteriovenosa del pulmón fué confirmado al operar y sanó con la neumonectomía.
5. Comunicase un nuevo caso de fístula arteriovenosa del pulmón.

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## DISCUSSION

JOHN C. JONES<sup>3</sup>

Shortly after Doctor Goldman published the report of his first case in his original communication on this subject, a patient was referred to us for surgery of a lung tumor which we diagnosed clinically before operation as being an arteriovenous aneurysm of the lung. This patient had all the clinical aspects of an arteriovenous fistula of the lung including a continuous murmur over the tumor itself. I wish only to emphasize, by showing slides of X-ray films and photographs of the specimen, how helpful planography is in the diagnosis, for, after all, it is obvious that this is a more common lesion than we suspected and angiocardiology is not universally available to help in the diagnosis. Planograms were very valuable to us as a confirming roentgen diagnosis and at least in this particular case there was no need for angiocardiology. Doctor Goldman has presented a most interesting aspect of the subject, namely the hereditary factor in this congenital lesion, and I can recommend your reading the full text of his excellent paper which could only briefly be presented here to-day.

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# PULMONARY ADENOMATOSIS<sup>1</sup>

Report of a Case

EUGENE HILDEBRAND<sup>2</sup>

Pulmonary adenomatosis is a rare disease in man. So far as the author knows, no cases have been reported from Montana. Because of the similarity of its pathology in man to that of Montana progressive pneumonia of sheep (*Jaag-ziekte*), the case is deemed worthy of reporting.

## CASE REPORT

The patient, a 66-year-old ranchwife, was seen at the Clinic in March, 1946, complaining of an unproductive cough of three months' duration. Coarse râles were noted throughout both lungs. A roentgenogram of the chest (figure 1) revealed a shadow extending laterally from the right hilum and a presumptive diagnosis of carcinoma of the lung was made.

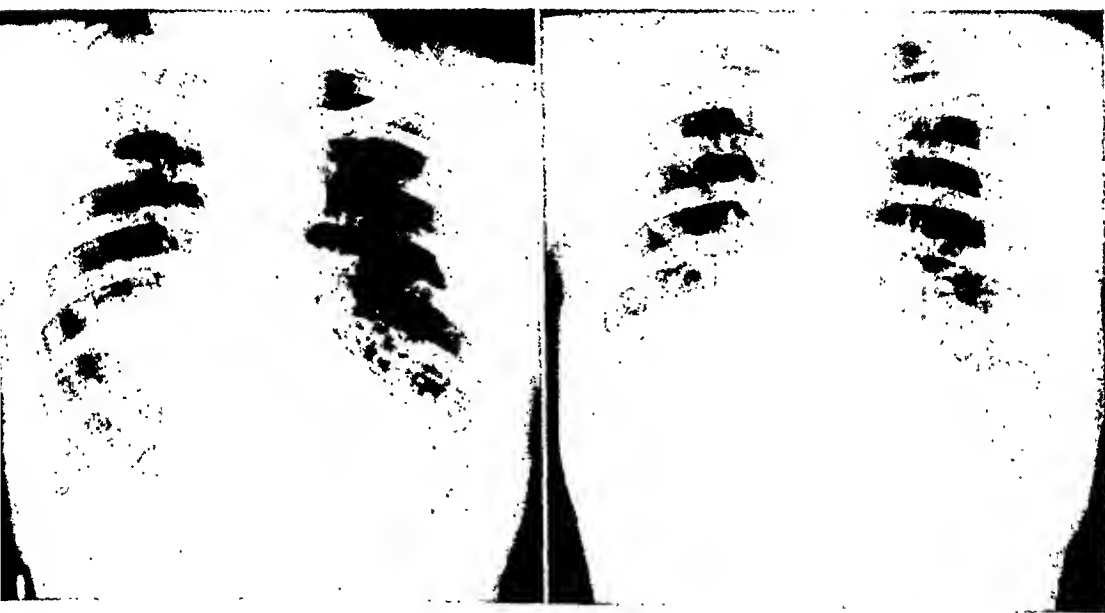


FIG. 1

FIG. 2

FIG. 1. (Left.) X-ray film of the chest taken in March, 1946, showing the mass at the right hilum.

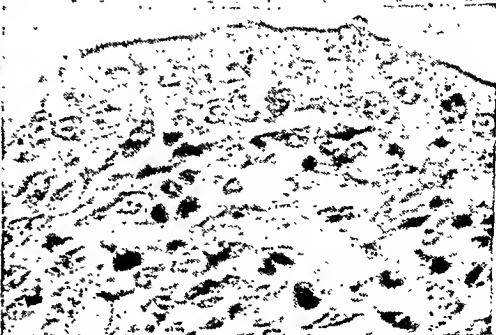
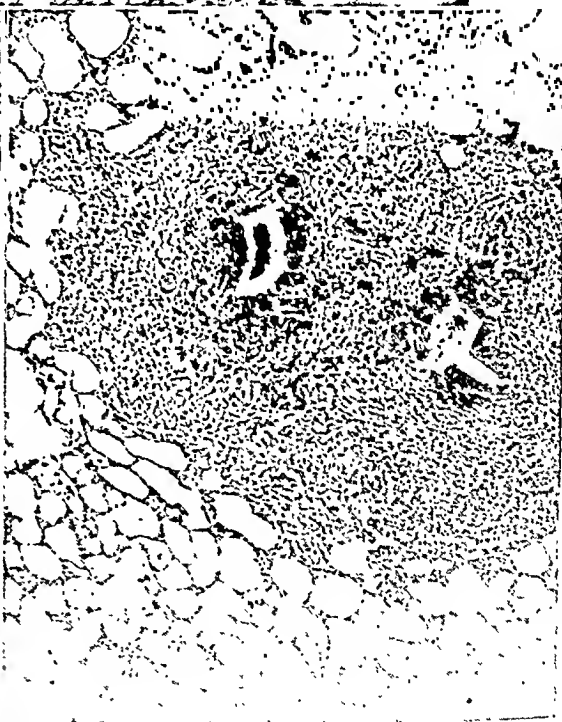
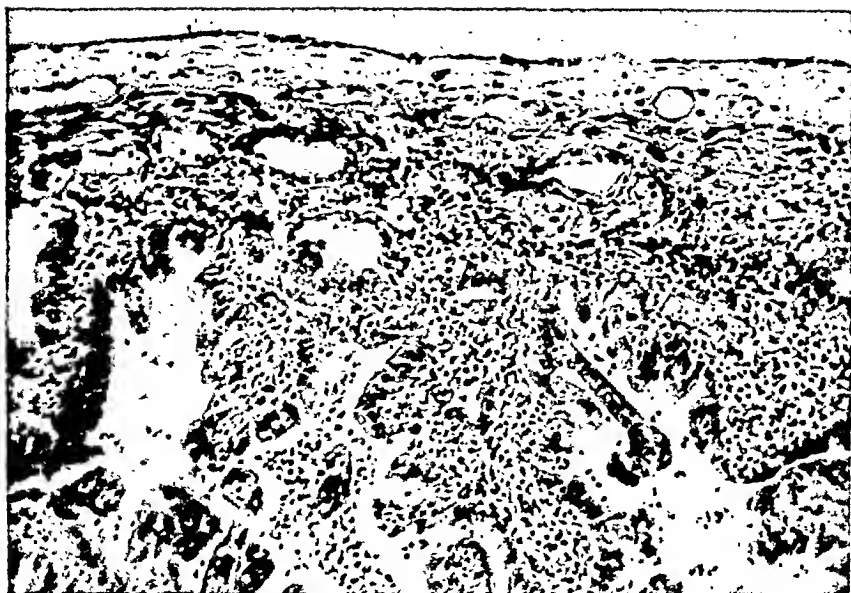
FIG. 2. (Right.) X-ray film of the chest taken in September, 1946, showing extension of the mass at the right hilum and involvement of the left lung.

Surgery was deemed inadvisable. She was given supportive and symptomatic treatment. Soon the cough became productive of clear frothy sputum. This sputum gradually

<sup>1</sup> Presented before the Medical Section, at the Clinico-Pathological Conference, at the 3rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 19, 1947.

<sup>2</sup> Great Falls Clinic and Montana Deaconess Hospital, Great Falls, Montana.





FIGS. 3-7

increased in amount so that finally great quantities were expectorated. It did not become purulent, however, and there was no hemoptysis. She became dyspneic and this dyspnea was progressive. There was no chest pain. Weakness was marked. The patient died of respiratory failure in September, 1946. Terminally the roentgenogram showed extension of the shadow at the right hilum, with apparent involvement of the left lung as well (figure 2).

*Necropsy findings:* The principal pathological change was confined to the heart and to the lungs. The heart revealed aortic stenosis and calcification, together with hypertrophy. The examination of the lungs was most interesting.

The left lung weighed 530 g. The surface was grayish-pink in color with moderate anthracosis. The upper lobe crepitated poorly. The consistency of the lower lobe was greatly increased. Cut surface of the upper lobe was reddish-brown in color and congested. Cut surface of the lower lobe was mottled grayish-brown with numerous small, irregular areas of apparent consolidation. Purulent appearing material ran from the bronchioles. The bronchi were filled with frothy gray fluid but otherwise showed no changes. The vessels appeared to be normal.

The right lung weighed 1,000 g. The consistency was moderately increased throughout. The upper and middle lobes resembled the left upper lobe except that occasional irregular areas of consolidation were found. The right lower lobe was similar to the left lower lobe. The bronchi were traced with extreme care. They were found to be uniformly dilated, the lower lobe bronchus showing the greatest degree of dilatation. The bronchi revealed no other significant abnormality. The vessels appeared to be normal.

Microscopic sections were taken from areas of apparent consolidation in the left lower lobe, right lower lobe, right middle lobe and right upper lobe. All areas were similar and revealed irregular spaces lined by tall columnar epithelium. These spaces branched and anastomosed. The lining cells were not dedifferentiated, and the basement membrane was everywhere intact. Rare mitoses were found. The spaces were filled with polymorphonuclear leucocytes (figure 3).

There was no evidence of metastases in the hilar nodes or elsewhere.

The diagnosis was: pulmonary adenomatosis, complicated by acute pneumonitis and bronchiectasis.

#### DISCUSSION

Only about a dozen cases of this rare disease have been reported in man. Among these are the cases of Helly (1), Obendorfer (2), Bonne (3), Richardson (4), Sims (5), Bell (6), Taft and Nickerson (2 cases) (7), Wood and Pierson (8), and Alexander and Chu (9). Neuburger and Geever (10), in their discussion of alveolar cell tumors, review other cases which may be similar. Simon (24, 25)

FIG. 3. (Upper.) Section through a consolidated area adjacent to the pleura (patient).

FIG. 4. (Centre left.) Low power photomicrograph showing areas of lymphocytic infiltration (chronic pneumonitis) and adenomatous proliferation in Montana sheep.

FIG. 5. (Centre right.) Very low power photomicrograph showing adenomatous proliferation surrounded by a zone of inflammation and fibrosis occurring in otherwise normal appearing lung in Montana sheep.

FIG. 6. (Lower left.) Intermediate power photomicrograph of periphery of adenomatous area showing adjacent fibrosis and inflammation in Montana sheep.

FIG. 7. (Lower right.) High power photomicrograph showing cellular detail of adenomatous process in Montana sheep.

believes pulmonary adenomatosis to be a variety of primary alveolar carcinoma. The etiology is obscure. It is thought by most observers that this probably is a neoplastic growth which may originate as metaplasia of alveolar cells. Other workers feel that it may originate from a downgrowth of bronchiolar epithelium.

Too few cases of pulmonary adenomatosis have been reported to cite characteristic symptoms. However, cough is frequently mentioned, dyspnea is a prominent symptom, and the production of white frothy nonpurulent sputum and loss of weight are also mentioned. Hemoptysis is reported in 3 cases (8, 9, 25), and chest pain in 4 (3, 5, 9, 25). The disease has been reported between the ages of 21 and 79, and both sexes appear to be affected equally. The average duration of the disease is reported by Alexander and Chu (9) as nine months, although Obendorfer's (2) patient died after a brief illness and Bell's (6) patient lived two and one-half years after pulmonary symptoms of cough and dyspnea developed. In most instances the diagnosis was made at autopsy. However, the diagnosis in Wood and Pierson's (8) case was made following lobectomy. Major (11) reported the disease in a negress. He made the diagnosis following pneumonectomy.

The case presented here conforms to the nonspecific clinical pattern noted above—a chronic disease of nine months' duration, gradually progressive, with cough, frothy white sputum, dyspnea and weakness being outstanding. The signs and symptoms noted above are quite similar to those seen in sheep suffering from *Jaagziekte*. These sheep usually will reveal signs and symptoms of increasing dyspnea and cough. White frothy sputum will run from the mouth and nostrils when the head is lowered. Emaciation is a late development. The disease is fairly common in certain locations, but seems to be geographically limited to South Africa, Iceland, England, France and the Rocky Mountain area of the United States. In these widely scattered localities the disease is known by a variety of names. In South Africa it is known as "*Jaagziekte*" or the "Drive Sickness;" in Iceland, it is known as "epizootic adenomatosis;" in England as "verminous pneumonia;" in France as "*La bouhite*" (12); in the Rocky Mountain area of the United States as "progressive pneumonia" or "lunger disease." In Montana, the disease is not only found among the domestic sheep but also among the bighorn sheep (13).

The disease has been known for many years in South Africa, as so well reported by Cowdry (14), but was unknown in Iceland until 1934 at which time an epidemic began which caused great economic losses, 60 per cent of a flock being lost in some cases, as reported by Dungal (15). Dungal and his associates found that sheep of the Gottorp strain were susceptible to the disease, whereas sheep of the Adalbol strain were relatively resistant. They found artificial transmission of the disease to be difficult, but the disease can be transmitted from affected sheep to healthy ones. Such transmission has also been observed in Montana by Marsh (13) when affected sheep and healthy ones were housed together. Verminous pneumonia in England presents a similar picture, both clinically and pathologically, except that often (but not always) the disease is associated with infestation by *Muellerius capillaris* (M'Fadyean (16), Dungal (15), Taylor (17)). Progressive pneumonia of sheep has been reported by Cowdry and Marsh (18) as

being similar to *Jaagziekte*. In my opinion, from a study of slides kindly supplied by Doctor Marsh, the epithelial proliferation is not as marked in the Montana disease as in the Icelandic or South African varieties. In the Montana disease, however, there is much more marked chronic interstitial pneumonitis early in the disease, followed later by rather marked fibrosis (figures 4, 5, 6 and 7). This is not seen to such a great extent in the Icelandic or South African varieties. Marsh agrees (13), and now believes that there may be different strains of the same disease, or that perhaps different animals possess different degrees of immunity. *Jaagziekte* is thought by many to be due to a virus. Wood and Pierson (8) consider that pulmonary adenomatosis of man also may be due to a virus infection. Dungal (19) states that he has seen no human cases in Iceland, not even among the shepherds, and states that "we must conclude that man is immune to this particular virus."

It is interesting to note that *Jaagziekte* has not been transmitted to common laboratory animals (Dungal (19)), although lesions similar to *Jaagziekte* have been described in guinea pigs inoculated with a diphtheroid bacillus isolated from a case of Hodgkin's disease (Grumbach (20)). Similar lesions are described by Olafson and Monlus (21) in toxoplasmic pulmonary infection in a cat. Grady and Steward (22) produced similar alveolar growths in mice by injection of carcinogens. Theiler (23) describes *Jaagziekte* in horses in South Africa. This was found to be due to the ingestion of a poisonous plant (*Crotalaria dura*), but is now rarely found since the plant growth has been controlled.

#### COMMENT

It will be noted that the patient was a ranchwife. She lived most of her life on a large sheep-ranch in Montana where *Jaagziekte* is endemic. However, for several years just prior to her last illness she lived in town and visited the ranch for vacations only. She was on the ranch for two weeks in the fall of 1945. The pulmonary symptoms began in December, 1945. Progressive pneumonia has been endemic on this ranch. A sheep from this ranch with signs and symptoms of the disease was killed in April, 1947, and at autopsy all lobes of the lungs were found to be involved in the inflammatory and adenomatous process. The possible common origin of the human and the sheep diseases is interesting to contemplate.

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# THE EFFECT OF DIET ON EXPERIMENTAL TUBERCULOSIS OF MICE<sup>1</sup>

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While studying the effect of different environmental factors on the susceptibility of mice to infection with mammalian tubercle bacilli, we observed that the severity and outcome of the disease were markedly influenced by the nature of the diet fed to the animals during the course of the experiment. As will appear from the results to be described in the following pages, it is possible, indeed likely, that the observed effects were due, not to a well defined dietary deficiency, but rather to a nonspecific physiological disturbance. Consequently, our findings, in their present exploratory form, are of little or no significance for the understanding of the relation of nutrition to tuberculous disease. Nevertheless, the enhancing effect of certain empirical diets on the susceptibility of mice was so consistent and striking, that it has been used in our laboratory for the establishment of infection with minimal doses of cultures or with tuberculous sputum. We are presenting our preliminary results therefore, not as a nutritional study, but as a contribution to the technique of producing experimental tuberculosis in mice.

## MATERIALS AND METHODS

Mice were inoculated intravenously (caudal vein) or intracerebrally with graded amounts of cultures of the mammalian strain of tubercle bacillus H37Rv, grown in Tween-albumin liquid medium. Three strains of mice were used, line 1 dba, Swiss albino and Rockefeller Institute albino; the animals were 4 to 6 weeks old at the time of inoculation. The history of the culture used for infection, the composition of the medium and the origin and care of the animals have been described in a recent publication (1).

For at least one week prior to infection, the diet for all mice consisted of a single daily feeding of white bread soaked in whole milk. On the day before infection, the animals were transferred to metal cages (described in (2)) or to glass jars (described in (1)) and were then placed on the new experimental diet which was offered *ad lib*. Water was supplied from a drinking bottle with all diets. Each group of 4 or 6 mice (or of survivors thereof) was weighed as a group at the beginning of the experiment and at weekly intervals thereafter. Records of the dead animals were taken daily and autopsies performed on all of them as well as on the survivors at the end of the experiment.

## RESULTS

*Experiment 1:* As will be noted later, the bread and milk diet occupies an intermediate position among those diets which have been tested in our laboratory for their effect on the resistance of mice to experimental tuberculous infection. Since all animals were kept on this regimen before being changed to other experimental diets, it appeared useful, for purposes of comparison, to maintain some of the mice, both infected and uninfected, on the usual bread and milk mixture

<sup>1</sup> From the Laboratories of the Rockefeller Institute for Medical Research, 66th St. and York Ave., New York 21, New York.

throughout the experiment, and to compare their behavior with that of animals transferred to an even less favorable diet.

The experiment involved 24 mice of the line 1 dba strain (5 weeks old) and 24 Swiss albino (4 weeks old). Half of the animals in each group were fed the usual bread and milk mixture throughout the test; the others received a diet prepared as follows: 100 g. of cornmeal was thoroughly mixed with 5 g. of butter and 2 g. of salt mixture.<sup>2</sup> To this was added, with constant stirring, 100 cc. of 10 per cent gelatin in boiling water. The mixture was allowed to cool and solidify in the ice box and was distributed in amounts of 5 to 7 g. daily per mouse.

TABLE 1a  
*Effect of diet on susceptibility of dba mice to tuberculous infection*

WEEK AFTER INFECTION	CORNMEAL, GELATIN AND BUTTER DIET				BREAD AND MILK DIET			
	Uninfected controls		0.000,015 mg. H37Rv, i.v.		Uninfected controls		0.000,015 mg. H37Rv, i.v.	
	Average weight	Deaths (days after infection)	Average weight	Deaths (days after infection)	Average weight	Deaths (days after infection)	Average weight	Deaths (days after infection)
0	17.5		17.4		17.5		17.8	
1	14.6		14.0		19.0		18.2	
2	12.5		12.0		17.0		17.8	
3	13.0		11.1	20	16.7		17.3	
4	13.6		9.4	27, 27, 27	17.8		18.0	26
5	12.5		12.5	30, 30, 30	18.0		18.1	
6	15.8		11.5		18.2		19.8	39
7	15.8			44	18.3		25.5	47, 47
8	15.8		Average survival time 29 days		19.7		23.2	
9	15.0				19.5		21.8	66, 66
10	16.3				20.0		24.0	74
11	16.3				20.5		21.0	86
							Average survival time 58 days	
12	16.6				21.3			
13	18.0				21.9			

In each case, 8 of the animals (two groups of 4) were inoculated by the intravenous route with 0.000,015 mg. of culture (dry weight); the other 4 animals were held as uninfected controls. All of them were kept in glass jars throughout the experiment.

The weekly average weights and the time of death are recorded in tables 1a and 1b.

The results presented in tables 1a and 1b show that, irrespective of diet, mice of the line 1 dba strain were much more susceptible to experimental infection

<sup>2</sup> The salt mixture has the following composition: KCl, 42.5 g.; Na<sub>2</sub>CO<sub>3</sub>, 42.5 g.; MgCO<sub>3</sub>, 14.3 g.; CaCO<sub>3</sub>, 25.0 g.; ferric ammonium citrate, 5.5 g.

with culture H37Rv than were the Swiss albino animals, thus confirming previous findings reported elsewhere (1).

In the dba animals, the effect of nutrition on the course of infection became obvious very early; 7 out of 8 of those fed the cornmeal-gelatin-butter mixture were dead within thirty days after infection, at a time when there had been only one death on the bread and milk diet. The average survival time was twenty-nine days in the former and fifty-eight in the latter.

Swiss albino mice on the cornmeal-gelatin-butter diet began to show evidence of disease (loss of weight, as compared with the noninfected controls) during the second month of the experiment and 5 deaths occurred between the sixty-fourth

TABLE 1b  
*Effect of diet on susceptibility of albino Swiss mice to tuberculous infection*

WEEK AFTER INFECTION	CORNMEAL, GELATIN AND BUTTER DIET				BREAD AND MILK DIET			
	Uninfected controls		0.000,015 mg. H37Rv, i.v.		Uninfected controls		0.000,015 mg. H37Rv, i.v.	
	Average weight	Deaths (days after infection)	Average weight	Deaths (days after infection)	Average weight	Deaths (days after infection)	Average weight	Deaths (days after infection)
	g.		g.		g.		g.	
0	22.3		21.8		22.0		22.0	
1	19.3		20.0		21.5		21.6	
2	17.3		17.1		22.9		23.1	
3	17.3		16.7		24.2		24.6	
4	18.0		16.5		24.4		25.0	
5	18.5		17.1		27.0		27.0	
6	19.5		17.0		24.4		25.4	
7	17.9		15.8		26.7		26.1	
8	17.5		15.2		27.5		26.4	
9	19.0		14.3	64, 67, 69	26.3		25.0	
10	19.7		14.9	72	26.3		24.3	
11	19.3		14.4	80	27.3		24.7	
12	19.3		14.8		27.5		24.2	
13	19.8		14.6		29.0		25.8	

and eightieth day after infection. The infected albino mice fed the bread and milk mixture were all alive, weighed almost the same as the uninfected controls and appeared normal in behavior at the end of the experiment (fourteen weeks), although they exhibited numerous pulmonary lesions when sacrificed at that time.

None of the noninfected controls died in the course of the experiment. It must be noted, however, that the animals (albino as well as the dba) transferred from the bread and milk to the cornmeal-gelatin-butter diet lost up to 30 per cent of their original weight during the first four weeks. From that time on, the weight of the noninfected controls increased steadily, while that of the infected animals decreased steadily and rapidly until death.

*Experiment 2:* Among the different experimental diets used in the course of



the present study, the cornmeal-gelatin-butter mixture has proved one of the most effective in decreasing the resistance of mice to experimental infection with mammalian tubercle bacilli. The following experiment was therefore devised to test whether gelatin itself was responsible for enhancing the infection.

Diet #100 is a mixture of 66 per cent ground whole wheat, 33 per cent whole milk and 1 per cent salt (2). To 100 g. of this mixture were added 100 cc. of 10 per cent gelatin (dissolved in boiling water). The cornmeal-gelatin-butter diet was prepared as described under experiment 1. The third diet was identical with the latter except that, instead of a 10 per cent gelatin solution, water was added to the cornmeal-butter mixture. Mice

TABLE 2

*Effect of addition to diet of 10 per cent gelatin on susceptibility of mice to infection with H37Rv (intravenous injection)*

STRAIN OF MOUSE	INFECTION DOSE	DIET	SURVIVAL (S) OR DEATH (INDICATED BY NUMBER OF DAYS AFTER INFECTION)	NUMBER OF DEATHS TOTAL INFECTED
	mg.			
dba	0.0015	Cornmeal and butter	26, 26, 28, 28, 28, 28, 28, 28	8 8
	0.0015	Cornmeal, gelatin and butter	24, 25, 25, 25, 25, 26, 26, 28	8 8
	0.0015	Sherman 100 and gelatin	28, 28, S, S, S, S, S, S	2 8
Rockefeller Institute albino	0.015	Cornmeal and butter	15, 17, 17, 24, 26, 26, 26, 28 28, 30, 30, 30, 33, 33, S, S	14 16
	0.015	Cornmeal, gelatin and butter	12, 12, 16, 16, 16, 16, 18, 18 21, 21, 24, 26, 26, 28, 28, 29	16 16
	0.015	Sherman 100 and gelatin	18, 22, 26, S, S, S, S, S S, S, S, S, S, S, S, S	3 16

of the Swiss albino and line 1 dba strains (4 weeks old) which had been kept on the usual bread and milk mixture were transferred to the three experimental diets and were infected the following day by the intravenous route with the culture H37Rv as indicated in table 2.

The results reported in table 2 show that, in general, mice fed the cornmeal-butter mixture survived a few days longer than those receiving the same diet to which gelatin had been added; this slight difference may be significant since it has also been recognized in two other experiments. It is clear, however, that gelatin does not exhibit any gross effect on infection since, with both strains of mice and under the conditions of the experiment, the fatality rate was very low when the animals were fed a mixture of whole wheat and milk to which had been added an equal weight of 10 per cent gelatin solution.

Large numbers of experiments, carried out over a period of ten months, have been consistent in showing that the empirical diets which we have used fall into the following descending order with regard to effectiveness in permitting mice to resist the experimental disease resulting from the intravenous injection of tubercle bacilli.

Diet #100 (66 per cent whole wheat, 33 per cent dried milk, 1 per cent sodium chloride), with or without 10 per cent gelatin.

Fox chow pellets.

Mixture of white bread and whole milk.

Mixture of 85 per cent cornmeal, 5 per cent butter, 10 per cent gelatin and salts.

Naturally, attention has been given to the fact that the cornmeal diet is somewhat deficient in some of the essential amino acids and known vitamins. In a number of experiments, attempts were made to complement these diets by the addition of tryptophane, tyrosine, lysine, nicotinic acid and yeast extract, singly or in different combinations. In no case did the modifications improve the

TABLE 3

*Effect of diet on infection of Swiss albino mice with 0.005 mg. H37Rv by intracerebral route*

DIET	SURVIVAL (S) OR DEATH (INDICATED BY NUMBER OF DAYS AFTER INFECTION)	NUMBER OF DEATHS TOTAL INFECTED
#100 and gelatin.....	15,* 33, S, S, S, S	2 6
Cornmeal, gelatin and butter.....	21, 21, 22, 25, 26, 31	6 6

\* Probably accidental death.

resistance of the animals; indeed, it seemed as if in several cases more rapid death rates occurred with the supplemented diets.

*Experiment 3:* We have reported elsewhere that fatal tuberculosis, with extensive pulmonary involvement, can be brought about by infecting mice with mammalian tubercle bacilli by the intracerebral route (1). It is of interest, therefore, that this experimental disease can also be influenced by nutritional factors, as is shown in table 3.

Twelve Swiss albino mice, 4 weeks old, were infected by the intracerebral route with 0.005 mg. of H37Rv culture injected in a total volume of 0.03 cc.; 6 of them were fed diet #100 to which had been added 10 per cent gelatin (see experiment 2); the others received the cornmeal-gelatin-butter diet described in experiment 1. The animals were housed in metal cages with grids (minus bedding) throughout the experiment. The results are presented in table 3.

#### DISCUSSION

Contrary to general belief, there is little evidence, of either epidemiological or experimental nature, that nutritional factors have a significant effect on the

prevalence and severity of most infectious diseases (3, 4). In the case of tuberculosis, however, epidemiologists and clinicians believe that malnutrition, especially low protein intake, is clearly correlated with increase in mortality rates; moreover, there are a few experimental studies which suggest that vitamin deficiencies (especially of ascorbic acid and fat soluble vitamins) will decrease the resistance of guinea pigs and rats to tuberculous infection. The pertinent literature is reviewed in two recent textbooks and need not be discussed further at this time (5, 6).

The observations described in the present paper establish the fact that diet can have a profound effect on the susceptibility of mice to experimental infection with mammalian tubercle bacilli. This is the more interesting since high susceptibility has been observed with diets which are capable of supporting growth (even though not at optimum rate) and reproduction of uninfected animals, and which are adequate for the maintenance of mouse colonies. For example, striking differences in susceptibility have been observed by comparing a mixture of whole wheat and milk (most favorable for resistance to tuberculosis) with a diet consisting of cornmeal and butter supplemented with tryptophane, tyrosine, lysine, nicotinic acid and yeast autolysate, on which uninfected controls remained healthy but infected mice died of rapidly progressive disease.

At least three independent working hypotheses can be considered for the analysis of the nature of this nutritional effect on infection. It is possible that whole wheat or milk contain one or several substances—as yet unrecognized—which promote either natural resistance or the development of immunobiological protective mechanisms. On the other hand, cornmeal may increase the severity of the disease not negatively through a nutritional deficiency, but positively by supplying a factor which enhances infection. It is worth recalling in this respect that corn contains a pellagrigenic factor—probably indole acetic acid—the effect of which can be corrected by nicotinic acid (7, 8). Of special interest for the present discussion is the discovery in certain natural foodstuffs of a factor which decreases the resistance of mice to experimental pneumococcus infections (9, 10). It has also been reported that rabbits inoculated with bovine tubercle bacilli survive longer on a highly polished rice diet than on unpolished rice (11). Finally, it must be emphasized that those diets which have been found to decrease resistance to tuberculosis in our experiments have also caused a rapid loss of weight of the animals at the time of, and for three weeks after, transfer from bread and milk to the experimental regimen. It is true that, following this initial loss of weight, the uninfected controls began to regain weight and apparently remained normal and healthy thereafter. Nevertheless, the findings suggest that the increased susceptibility to infection observed with certain regimens may not be due to any particular dietary factor, but rather to a nonspecific physiological disturbance affecting the unknown host factors which condition resistance to tuberculous infection. It is of interest in this respect that, when rats or mice are infected with *Salmonella typhi-murium*, bacterial invasion occurs more rapidly when the food intake is progressively reduced to 70 per cent of the optimum level (12).

## SUMMARY

The survival time of mice infected with mammalian tubercle bacilli is markedly affected by the composition of the diets fed to the animals during the course of the experiment. Of the diets tested, a mixture of whole wheat and dried milk was the most favorable for resistance to infection, and a mixture of cornmeal and butter the most unfavorable. The differences could be recognized with several strains of mice whatever the infective dose, and the route of infection used for the infection test.

## SUMARIO

*La Alimentación en la Tuberculosis Experimental del Ratón*

El tiempo de sobrevivencia de los ratones infectados con bacilos tuberculosos de mamífero se ve notablemente afectado por la composición de las dietas suministradas durante el experimento. De las dietas ensayadas, una mezcla de trigo íntegro y leche seca resultó ser la más favorable para evocar resistencia a la infección, y una mezcla de harina de maíz y mantequilla, la más desfavorable. Independiente de la dosis infectiva y de la vía de infección utilizada en el ensayo, pudieron reconocerse las diferencias mencionadas en varias cepas de ratones

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# CHEMISTRY OF THE LIPIDS OF TUBERCLE BACILLI

LXXIV. A Contribution to the Study of Acid-fastness of Acid-fast Bacilli<sup>1</sup>

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The term acid-fastness as applied to acid-fast bacilli may be defined as the property of these bacilli when once stained by carbol fuchsin to resist destaining on treatment with acids or alcohol. There has been much discussion and speculation concerning the nature of acid-fastness, and various theories have been proposed to account for this phenomenon. Some investigators regard acid-fastness as being due to physical conditions (1, 2) which depend upon the degree of dispersion or aggregation of the protoplasmic micelles.

As the knowledge of the chemical composition of the tubercle bacillus increased various chemical theories were advanced to account for acid-fastness. Thus it was believed that a form of cellulose (3) or a protein-cellulose complex<sup>4</sup> (4) or even a protein substance similar to chitin (5) was responsible for the acid-fastness of the bacilli. Other investigators regarded certain of the lipid substances present in the bacillus (6, 7, 8,) as the cause of acid-fastness. Roux and Borrel (9) demonstrated that tubercle bacilli, after treatment with dilute hydrochloric acid and extraction with hot xylene, were not acid-fast, whereas the lipid substances in the extract exhibited distinct acid-fast properties. Bulloch and MacLeod (10) extracted tubercle bacilli with hot methyl alcohol and showed that the only substance possessing acid-fastness was that portion of the lipids which was insoluble in cold methyl alcohol. These investigators, after saponification of the lipids, isolated a substance in the form of a white powder which they considered to be a higher alcohol and which was also found to be acid-fast. Tamura (11) isolated a substance, which he named *Mykol*, regarded as a higher alcohol and which was acid-fast. In investigations reported by Macheboeuf, Levy and Fethke (12) it was shown that acid-fast substances could be extracted from tubercle bacilli by neutral solvents without subjecting the lipids to saponification.

Acid-fastness is not limited to the group of so-called acid-fast bacilli (13). Acid-fast compounds have been detected in the lungs in some cases of lipid pneumonia (14, 15, 16), while analogous compounds called ceroids have been observed in the livers of rats fed diets deficient in choline, protein and vitamin E (17, 18). These acid-fast compounds seem to be derived from oxidation prod-

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<sup>4</sup> Unpublished results of experiments in this laboratory have failed to reveal any cellulose in the tubercle bacillus. The only cellulose that was discovered were paper fibers derived from filter papers used in filtering large quantities of bacillary cells.

ucts of unsaturated fats, since in experimental studies *in vivo*, injections of unsaturated fats have resulted in deposits of acid-fast material in the tissues (19, 20, 21). Similar changes have been observed under suitable experimental conditions *in vitro* (22, 23). However, acid-fast substances, such as those mentioned above, differ entirely from the acid-fast compounds contained in the tubercle bacillus and in other acid-fast bacilli.

The investigations of Anderson and coworkers (24, 25, 26, 27) have shown that the only acid-fast compound isolated from the human type of the tubercle bacillus is mycolic acid. Mycolic acid is a saturated optically active acid with an average molecular weight, determined by titration, of 1,284 and a melting point of 55° to 56°C. The structure of mycolic acid has not been established, but it has been shown that it contains one hydroxyl and one methoxyl group to one carboxyl and that the simplest formula calculated from its composition is  $C_{88}H_{176}O_4$ . Mycolic acid, when heated under reduced pressure to a temperature above 250°C., decomposes, yielding n-hexacosanoic acid,  $C_{26}H_{52}O_2$ , and a neutral non-volatile unsaturated residue.

Since mycolic acid is the only acid-fast substance that has been found in the lipid compounds extracted from the tubercle bacillus, it might be assumed that mycolic acid is responsible for the acid-fastness of the intact cells of the bacilli (28), but many inconsistencies have been described in the staining behavior of the bacillus (29, 30, 31, 32, 33) which cast some doubt on mycolic acid as being solely responsible for the acid-fastness of the bacillus. For instance, it remains unexplained why the mere disintegration of the bacterial cells by grinding in a mortar or between glass slides renders the bacterial mass non-acid-fast, since mycolic acid would still be present in the bacterial residue. The acid-fastness of the bacilli cannot be removed by exhaustive extraction with neutral solvents, for after such treatment the cells retain a certain amount of lipid constituents that are very firmly bound in the cellular structure. The firmly bound lipids can be removed, however, after the partly defatted cells have been treated with dilute acid according to the Aronson procedure (34), followed by exhaustive extraction with ether and chloroform. The bacterial residue after this treatment is non-acid-fast. It has been shown (35) that the firmly bound lipids contain mycolic acid which is liberated on saponification. It would appear, therefore, that when all lipids containing mycolic acid are removed from the bacilli, acid-fastness is also removed. This fact would indicate that mycolic acid is intimately associated with the state of acid-fastness of the bacilli.

The results reported in this paper present certain data, which may be used to review theoretical considerations concerning the structure of the tubercle bacillus. They may serve to reconcile previously reported inconsistencies in its staining properties and perhaps explain how acid-fastness could be lost on grinding. For lack of experimental data on this subject, however, the discussion will be reserved for a later publication.

The present study was planned to determine whether other lipid substances besides mycolic acid that could be extracted from the tubercle bacillus possessed the property of acid-fastness. The results that we have obtained confirm previ-

ous statements that mycolic acid is the only acid-fast substance present in tubercle bacilli. The results indicate moreover that the various lipid fractions possess the property of acid-fastness in the proportion in which they contain free, that is, non-esterified, mycolic acid.

In addition to the mycolic acid of the human tubercle bacillus we have examined the staining properties of analogous mycolic acids isolated from other strains of acid-fast bacilli and have found that these acids behave in a manner similar to mycolic acid. We have also investigated the staining properties of various naturally occurring higher fatty acids and higher alcohols, but none of the compounds examined has shown any acid-fastness. However, when these compounds were combined with mycolic acid varying degrees of acid-fastness were observed, depending upon the proportion of mycolic acid that was present in the mixture.

Finally, various derivatives of mycolic acid were tested for acid-fastness, such as the acetyl derivative and the methyl ester of mycolic acid. Since it was found that the acetyl derivative was acid-fast but that the methyl ester was non-acid-fast, it would appear that the carboxyl group is mainly responsible for acid-fastness.

#### EXPERIMENTAL

The materials used in this study of acid-fastness, in the first place, consisted of various chemical compounds isolated in this laboratory from tubercle bacilli and other acid-fast bacteria; second, derivatives of mycolic acid and closely related hydroxy acids were investigated. For comparison we tested several chemical compounds, such as higher fatty acids and alcohols isolated from natural sources, together with certain synthetic compounds prepared especially for these tests.

In preparing the films on the microscopic slides the most satisfactory method was found to be to melt carefully the substances on the slides and to spread the melted substance evenly into a thin film with a cover glass. Attempts to prepare films by evaporating solutions of the substances on the slides did not result in uniform films. In order to stain the films the slides were immersed in a solution of carbolfuchsin warmed to a temperature of 40° to 45°C. for a period of twenty minutes. Preliminary experiments showed that at room temperature the films were not stained even after a period of forty-eight hours. The destaining was accomplished at room temperature by placing the slides in a 25 per cent solution of nitric acid for twenty minutes and afterwards for the same time in 95 per cent of ethyl alcohol.

At first a number of lipid fractions isolated from the human tubercle bacillus were tested for acid-fastness by the technique indicated above. The results are presented in table 1.

It is evident from the data presented in table 1 that certain lipid fractions of the tubercle bacillus do not exhibit acid-fastness, whereas other fractions are strongly acid-fast. Among the non-acid-fast compounds are the phosphatides, the purified wax, the alcohol phthiocerol and the neutral substance. The

strongly acid-fast compounds are mycolic acid, the so-called unsaponifiable wax and the soft wax. In the latter two fractions mycolic acid is a prominent constituent. The slightly acid-fast properties of fraction 8 and fraction 12 probably depend upon their content of mycolic acid. It is surprising that the purified wax, which on saponification yields about 50 per cent of mycolic acid, is non-

TABLE 1

*Acid-fastness of lipid fractions isolated from the human tubercle bacillus*

NUMBER OF FRACTION	SUBSTANCE TESTED	STAIN BY CARBOL FUCHSIN SOLUTION	AFTER DESTAINING WITH	
			25 per cent nitric acid	95 per cent alcohol
1	Phosphatide from strain H37 (36, 37)	++	+	0
2	Phosphatide from cell residues from tuberculin (38, 39)	++	+	0
3	Soft wax from strain H37 (40)	+++	++	++
4	Purified wax, strain H37 (41)	++	+	0
5	Phthiocerol (42, 43, 44)	+	0	0
6	Mycolic acid (27)	+++++	+++++	+++++
7	Crude unsaponifiable wax <sup>5</sup>	+++++	+++++	+++++
8	Residue in mother liquors from unsaponifiable wax <sup>5</sup>	+++	++	+
9	Mycolic acid from bacilli grown on dextrose containing medium <sup>6</sup>	+++++	+++++	+++++
10	Mycolic acid from cell residues from tuberculin <sup>7</sup>	+++++	+++++	+++++
11	Neutral substance, m.p. 70°, separated from mycolic acid	+	0	0
12	Ether-insoluble wax from cell residues from tuberculin	+++	++	++

The symbols used above have been chosen to represent the visual effect rather than an exact measure of acid-fastness. Thus, +++++ = very strong; ++++ = strong; +++ = considerable; ++ = slight; + = very slight; 0 = none.

acid-fast. As will be mentioned later, it is reasonable to assume in the case of this compound that the functional groups of mycolic acid which are responsible

<sup>5</sup> The purified wax, fraction 4, obtained from the chloroform extract, yielded upon saponification under mild conditions at room temperature about 50 per cent of crude unsaponifiable wax, fraction 7. After drastic saponification and precipitation from ethereal or benzene solutions by addition of alcohol or acetone, mycolic acid, fraction 6, was obtained. Fraction 8 represented the residue contained in the mother liquors on purification of mycolic acid.

<sup>6</sup> The mycolic acid had been isolated in the usual way, but the bacilli had been cultivated on a medium in which dextrose had replaced glycerol.

<sup>7</sup> The bacterial cells that were extracted were residues from the preparation of tuberculin. The mycolic acid, fraction 10, was obtained from the chloroform-soluble wax by drastic saponification. In the purification of the mycolic acid two ether-insoluble fractions were isolated. Fraction 11 was a neutral substance, whereas fraction 12 was acidic with a neutral equivalent of about 1700.



for the property of acid-fastness are in firm chemical combination with other components of the wax.

Since the acid-fastness of the lipids of the tubercle bacillus appears to depend upon the presence of free mycolic acid, we examined various derivatives of mycolic acid in which the hydroxyl group and the carboxyl group were substituted. The results are recorded in table 2.

The data presented in table 2 show that the acetyl derivative and iodomycolic acid are strongly acid-fast, and this fact would indicate that the hydroxyl group of mycolic acid is not responsible for the acid-fastness. That the potassium salt of mycolic acid is also acid-fast is not surprising because some ionization would

TABLE 2  
*Acid-fastness of derivatives of mycolic acid*

NUMBER OF FRACTION	SUBSTANCE TESTED	STAIN BY CARBOL FUCHSIN	AFTER DESTAINING WITH	
			25 per cent nitric acid	95 per cent alcohol
13	Acetyl derivative of mycolic acid	+++++	+++++	+++++
14	Iodomycolic acid	+++++	+++++	+++++
15	Potassium salt of mycolic acid	+++++	+++++	+++++
16	Amide of mycolic acid	0	0	0
17	Methyl ester of mycolic acid	+	0	0
18	Acetyl derivative of the methyl ester of mycolic acid	+	0	0
19	Non-volatile residue from pyrolysis of mycolic acid	+++	+++	+++
20	Non-volatile residue + hexacosanoic acid 3:1	+	+	+
21	Paraffin + mycolic acid 1:1	+	+	+
22	Paraffin + mycolic acid 9:1	+	0	0
23	Stearic acid + mycolic acid 1:1, 3:1, 9:1	+++++	+++++	+++++
24	Hexacosanoic acid + mycolic acid 9:1, 49:1	++	+	+
25	Hexacosanoic acid	+	0	0

occur in the staining solution and hence the staining of a neutral salt such as the potassium salt would depend upon the pH of the solution.

In the case of the amide and the methyl ester of mycolic acid, however, the conditions are entirely different, for in these compounds the carboxyl group is more firmly neutralized. Since these substances are not acid-fast, it is evident that the free carboxyl group is essential for acid-fastness.

It has been shown in earlier publications (25) that, when mycolic acid is heated above 250°C. in a vacuum, the acid undergoes pyrolysis and it is split into normal hexacosanoic acid which distills off, leaving a neutral non-volatile residue. These cleavage products were tested separately and in combination. It will be noted that the non-volatile residue showed some acid-fastness, but the hexacosanoic acid was not stained. When the residue was combined with hexacosanoic

acid approximately in the proportion in which they occur in mycolic acid, the mixture was found to be non-acid-fast. This fact would indicate that the configuration in the molecule of mycolic acid which is responsible for acid-fastness depends upon the chemical structure of the acid. When the original structure is broken during pyrolysis, a recombination, prepared by melting together the components, gives a mixture which possesses decidedly different properties.

TABLE 3

*Acid-fastness of compounds isolated from other strains of acid-fast bacilli*

NUMBER OF FRACTION	SUBSTANCE TESTED	STAIN BY CARBOL FUCHSIN	AFTER DESTAINING WITH	
			25 per cent nitric acid	95 per cent alcohol
Compounds from the bovine tubercle bacillus (45)				
26	Purified wax	+++++	+++++	+++++
27	Bovine mycolic acid, m.p. 56-58°	+++++	+++++	+++++
28	Bovine mycolic acid, m.p. 50-51°	+++++	+++++	+++++
29	Hexacosanoic acid, m.p. 80-82° separated as potassium salt from bovine mycolic acid	+	0	0
Compounds from the avian tubercle bacillus (46)				
30	$\alpha$ -Avian mycolic acid	+++++	+++++	+++++
31	$\beta$ -Avian mycolic acid	+++++	+++++	+++++
Compounds from the timothy grass bacillus (47)				
32	Phleimycolic acid dimethyl ester	+++	++	++
33	Residue on pyrolysis of No. 32	+++	+++	+++
34	Residue after saponification	+++++	+++++	+++++
Compounds from the so-called leprosy bacillus				
35	Leprosin from Papas strain <sup>a</sup>	+++++	+++++	+++++
36	Leprosin from Li strain <sup>a</sup>	+++++	+++++	+++++
37	Leprosin from Duval strain <sup>a</sup>	+++++	+++++	+++++
38	Firmly bound lipids, m.p. 170-180° (48)	+	0	0
39	Acetyl derivative of leprosinic acid	+++++	+++++	+++++
40	Leprosinic acid methyl ester	++	++	+

In view of the observations mentioned above, various combinations of mycolic acid and other substances were uniformly mixed by melting the components and then testing them for their staining properties. Mixtures of mycolic acid and paraffin or hexacosanoic acid were prepared in the proportions indicated in table 2. When these mixtures were subjected to the staining technique it was found that the acid-fast property of mycolic acid had practically disappeared. However, mixtures of mycolic acid and stearic acid were distinctly acid-fast. The

<sup>a</sup> Data concerning these three strains have not yet been published.

results obtained indicate that the presence of certain non-acid-fast compounds, such as paraffin and hexacosanoic acid, will mask the acid-fast property of mycolic acid.

*Acid-fastness of lipids of other acid-fast bacilli:* A series of compounds, analogous to those obtained from the human tubercle bacillus, which had been prepared from other acid-fast bacilli in this laboratory, were available and, for comparison, they were tested for acid-fastness in the manner described above. These compounds had been isolated from the bovine and avian types of tubercle bacilli, from the timothy grass bacillus and from the so-called leprosy bacillus. The results are recorded in table 3.

TABLE 4  
*Other compounds tested for acid-fastness*

NUMBER OF FRACTION	SUBSTANCE TESTED	STAIN BY CARBOL FUCHSIN	AFTER DESTAINING WITH	
			25 per cent nitric acid	95 per cent alcohol
41	Tetratriacontane, $C_{44}H_{90}$ <sup>9</sup>	+	0	0
42	Paraffin	+	0	0
43	Corn wax (49)	+	0	0
44	Myricyl alcohol (49)	+	0	0
45	Docosanoic acid (49)	+	0	0
46	Tetracosanoic acid (49)	+	0	0
47	Stearic acid	+	0	0
48	Stearyl alcohol	+	0	0
49	Stearylstearate	+	0	0
50	Dihydroxystearic acid	++	0	+
51	Cholic acid (Merck)	++	0	+
52	Desoxycholic acid (Merck)	++	0	+
53	Stearocholeic acid <sup>10</sup>	++	0	+
54	Methyl-3-acetoxycholenate (Merck)	++	0	+

It is apparent from the results presented in table 3 that acid-fastness is exhibited only by compounds analogous to mycolic acid and only the free acids show this staining property. The methyl esters prepared from the acids are not acid-fast.

For comparison with the staining properties of the lipids of acid-fast bacilli, which have been described above, we also examined a series of other lipid compounds, some of which had been isolated from natural sources and some that had been prepared synthetically. The experimental data are recorded in table 4.

It will be noted from the data recorded in table 4 that hydrocarbons, such as tetratriacontane and paraffin or corn wax and its cleavage products, namely, myricyl alcohol, docosanoic and tetracosanoic acids and also stearic acid, stearyl

<sup>9</sup> Normal tetratriacontane prepared by electrolysis of potassium stearate.

<sup>10</sup> Stearocholeic acid was prepared by dissolving 0.2 g. of stearic acid in alcohol and adding the solution to an alcoholic solution of 2 g. of desoxycholic acid. The crystalline stearocholeic acid that separated from the solution was recrystallized from alcohol.

alcohol and stearylstearate, are only slightly colored when stained by the Ziehl-Neelsen technique. It is evident also that all of these compounds are not acid-fast. On the other hand, dihydroxystearic acid, the cholic acids, and their derivatives, are more deeply stained by carbol fuchsin, but these substances are not acid-fast. The results indicate, however, that hydroxy acids of high molecular weight show a tendency to stain more deeply than neutral substances, such as hydrocarbons, wax and normal fatty acids, but all of these compounds are easily decolorized by nitric acid. In no case in the substances tested was acid-fastness observed comparable to that of mycolic acid.

#### DISCUSSION

As is well known, Koch (50) employed an alkaline solution of methylene blue for staining tubercle bacilli, while basic fuchsin mixed with an aqueous solution of aniline was recommended by Ehrlich (51). The staining solution now universally used was introduced by Ziehl (52) who added phenol to the fuchsin solution. Somewhat later Neelsen (53) recommended the use of a more concentrated carbol fuchsin solution. In order to obtain an acid-fast stain the addition of phenol to the fuchsin solution is essential. The phenol apparently forms a chemical combination with the fuchsin (54).

For destaining, Ehrlich (55) employed concentrated nitric acid diluted with two parts of water, and various concentrations of nitric acid have been used since that time. More recently a 10 per cent aqueous solution of sodium sulfite has been recommended for destaining (56, 57, 58), but in our hands we have found the classical method more specific.

Alcohol may act in two ways in the destaining process. Sometimes when a slide has been destained in nitric acid and then placed in alcohol the nitric acid is removed and the color on the slide reappears. On the other hand, substances which resist the action of nitric acid can be destained in alcohol. In this case the dye dissolves in the alcohol, leaving the slide colorless while the alcohol becomes colored red.

Acid-fastness of a substance depends upon its being stained by carbol fuchsin and retaining its color on subsequent treatment with nitric acid or alcohol. The mechanism involved in the destaining process is not clearly understood. Experience has shown, however, that substances which have been stained by carbol fuchsin are easily destained on treatment with nitric acid unless the dye has been firmly fixed or combined chemically with some group or groups in the molecule of the substance.

We have already pointed out in discussing the results reported in table 4 that hydrocarbons, esters, higher alcohols and higher normal fatty acids are only faintly stained by carbol fuchsin. This effect is apparently due to the weak adsorption of the dye on the surface of the film, hence the color is readily removed by nitric acid. The hydroxy acids tested in table 4 are stained more deeply and that is probably due to the polar groups present in these compounds, but nevertheless the dye must be loosely combined since the slides are easily destained in nitric acid. It is known that basic dyes are soluble in fatty acids (59) and it is

most probable that the dye forms a loose combination with the carboxyl group of the acid.

We have shown that the neutral methyl ester of mycolic acid is not acid-fast, whereas the free mycolic acid is strongly acid-fast. We have also shown that the purified wax of the tubercle bacillus, m.p. 215–218°, is not acid-fast, although on saponification the wax yields about 50 per cent of mycolic acid. The non-acid-fast character of the purified wax must be due to the fact that in this compound the carboxyl group of mycolic acid is firmly esterified with the polysaccharide or with the alcohol phthiocerol.

There is no explanation available to account for the acid-fastness of mycolic acid or of analogous hydroxy acids isolated from the bovine and avian tubercle bacilli or from the timothy grass bacillus and the so-called leprosy bacillus. These acids possess complex and as yet unknown chemical constitutions. In the case of every acid that we have studied we have found that the carboxyl group must be free in order that the mycolic acids exhibit the property of acid-fastness. Although the exact explanation of the acid-fastness is lacking, the experimental data are striking and convincing. The only acid-fast substances that we have been able to isolate from the tubercle bacillus and other acid-fast bacteria are the free mycolic acids.

#### SUMMARY

1. Ordinary chemical compounds of known constitution, such as hydrocarbons, higher normal fatty acids, esters, higher alcohols and hydroxy acids, are not acid-fast.

2. The only acid-fast substance that we have been able to isolate from extracts of the human tubercle bacillus is mycolic acid.

3. Analogous hydroxy acids, namely the bovine, avian and phleimycolic acids and leprosinic acid, are also acid-fast.

4. Derivatives of the mycolic acids in which the hydroxyl group is combined, as acetyl or iodo derivatives, are acid-fast.

5. The methyl esters of the mycolic acids are not acid-fast.

6. The free carboxyl group of the mycolic acids appears to be essential for acid-fastness.

#### SUMARIO

##### *Química de los Lípidos del Bacilo Tuberculoso*

1. Los compuestos químicos corrientes de composición conocida, tales como hidrocarburos, ácidos grasos normales más altos, ésteres, alcoholes más altos y ácidos del grupo hidroxilo no son ácidos resistentes.

2. La única sustancia ácidos resistente que pudieron aislar los AA. de extractos del bacilo tuberculoso humano, fué ácido micólico

3. Ácidos análogos del grupo hidroxilo, a saber, los ácidos bovino, aviario y fleiomicólico y el leprosinico, también son ácidos resistentes.

4. Son ácidos resistentes los derivados de los ácidos micólicos que combinan el grupo hidroxílico, tales como los derivados del acetilo o el yodo.

5. No son ácidorresistentes los ésteres metílicos de los ácidos micólicos.
6. El grupo carboxílico libre parece ser esencial para la ácidorresistencia.

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## THE DEATH REGISTRATION STATES

MARY DEMPSEY<sup>1</sup>

The statistical service of the National Tuberculosis Association is frequently asked to explain why nowadays the tuberculosis death rate in the United States for 1900 is quoted as 194 per 100,000 population, whereas in past years vital statisticians agreed that tuberculosis deaths in 1900 numbered 202 per 100,000 inhabitants.

The reason for this difference lies in the history and development of vital statistics in the United States. Prior to 1933 mortality data were not available on a country-wide basis because the registration of deaths was so incomplete in certain states as to be decidedly unreliable. As a result, the U. S. Bureau of the Census designated as the "death registration area" those sections of the country which had comparatively complete death registration; moreover, the Census Bureau based their published mortality statistics on this area which constantly expanded as death registration improved.

In 1900 the death registration area, consisting of ten states, the District of Columbia, and a number of large cities in the non-registration states, included 40.5 per cent of the population of continental United States. The population of this area was predominantly urban. Another important characteristic of the people in this original registration area was the high proportion of white persons residing in the more industrialized sections of the country. If cities in the non-registration states had been excluded, the population in the death registration states in 1900 would have represented but 26.2 per cent of the total population of the United States.

Prior to 1940 most of the national data published by the Bureau of the Census related to the death registration area. In that year, however, the historical series of vital statistics which was published for the United States prior to the completion of the registration area in 1933 was shifted from the basis of the registration *area* to that of the registration *states*. By basing mortality rates on the deaths from tuberculosis in the death registration *states* rather than on those which occurred in the registration *area*, a more nearly accurate picture is presented in that the findings are not unduly weighted by too exclusively a white industrial population living under urban conditions.

Prior to 1918 quite a noticeable difference was found each year between death rates based on mortality in the death registration *states* and those based on mortality in the death registration *area*. Beginning with the year 1918, however, this difference became negligible as the area expanded and in 1933 this problem was ended since all 48 states had by that time been admitted to the death registration area.

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*Tuberculosis death rates per 100,000 population in the death registration area and in the death registration states: 1900-1933\**

YEAR	TUBERCULOSIS DEATH RATES PER 100,000 POPULATION	
	Death registration area	Death registration states
1900	202	194
1901	197	190
1902	185	174
1903	189	177
1904	201	188
1905	192	180
1906	180	176
1907	179	174
1908	168	162
1909	161	156
1910	160	154
1911	159	155
1912	150	145
1913	148	144
1914	147	142
1915	146	140
1916	142	138
1917	147	144
1918	150	150
1919	126	126
1920	114	113
1921	99	98
1922	96	95
1923	93	92
1924	90	88
1925	87	85
1926	87	86
1927	81	80
1928	79	78
1929	76	75
1930	72	71
1931	68	68
1932	63	63
1933	60	60

\* Source: U. S. Bureau of the Census.

On July 1, 1946 the vital statistics division of the Bureau of the Census was transferred to the U. S. Public Health Service. The division is now known as the National Office of Vital Statistics.

# George Herbert Evans

1869-1947

George Herbert Evans was born in 1869 at Ontario, Canada. After local schooling he attended the Detroit College of Medicine and Surgery where he received the degree of Doctor of Medicine in 1891. In that same year he commenced practice in San Francisco. He followed his profession continuously in that city until his retirement from active practice in 1933.

Early in his career he became interested in tuberculosis and, while engaged primarily in the private practice of internal medicine, he always took an active part in any tuberculosis work, in San Francisco and in California and with the National Tuberculosis Association as well as with international organizations.

He was a delegate to the International Tuberculosis Congress in Paris in 1905. He was one of the founders of the San Francisco Tuberculosis Association and one of the original organizers of the first voluntary tuberculosis association of the State of California, now known as the California Tuberculosis and Health Association.

California, being a large state, is more or less divided into Northern and Southern sections. Through close personal friendship as well as sympathetic professional understanding, Doctor Evans represented and helped organize tuberculosis in the Northern part of the state, while Dr. Francis M. Pottenger was doing the same thing for Southern California. Over a period of many years they met at least monthly to discuss these and other affairs of mutual interest. In those days this required tedious train travel over a long weekend.

Doctor Evans was given charge of the so-called "Tuberculosis Colony" instituted by the San Francisco Department of Health in 1906. This marked the first attempt of the Municipality at the isolation of patients with active tuberculosis. It started as a few tents in the old County Hospital grounds at Ingleside. Doctor Evans was very fond of telling the story of his first resident who came to him wondering where he would find the early cases they were hoping for that were considered treatable. Doctor Evans instructed this young physician to "go over to the General Hospital and look through the wards for patients that are coughing, examine their sputum for tubercle bacilli and you will find enough cases to fill all of our few beds." It turned out to be just that way.

In 1908, while President of the California Medical Association, Doctor Evans initiated the movement which resulted in the formation of the Citizens' Health Committee which effected control of the bubonic plague epidemic then current in San Francisco. For many years he was the oldest living Past President of the California Medical Association.

In 1913 he was appointed Assistant Clinical Professor of Medicine at the University of California Medical School, to organize a Department of Tuberculosis, and up to 1933 he taught tuberculosis in that medical school through the wards of the San Francisco Hospital. He always approached the disease tuberculosis

as an important part of the field of internal medicine. His lectures to the junior and senior classes were carefully prepared and meticulously given, usually at the bedside of a patient. His personal acquaintance with the pioneers of modern antituberculosis work and his wide knowledge of existing institutions with his ability to illustrate and drive home a given point with an anecdote of a famous physician or a well known institution made his lectures alive and of great interest to the students. He took a real human interest in the members of his classes and



George Herbert Evans

1869-1947

went far out of his way to do the helpful personal things that an older physician can do for a neophyte, and also to instill the high ideals of the practice of medicine, of which Doctor Evans was a shining personal example.

Dr. George Evans together with Dr. Phillip King Brown, feeling the need of a private institution for the care of their own tuberculosis patients and knowing the necessity of having the many meticulous details in treatment carried out under their personal direction and according to their own ideas, founded, to this end, Alum Rock Sanatorium in the outskirts of San Jose. This has grown into

a nonprofit institution of wide services and usefulness and stands as another monument along his professional pathway.

Always active in medical society work, Doctor Evans was an ex-president of the San Francisco County Medical Society, the California Academy of Medicine, the California Tuberculosis Association and the American Therapeutic Society. He was also a fellow of the American College of Physicians and American Medical Association.

Since his retirement in 1933, he spent much of his time abroad in studies on tuberculosis, medical history and housing. When World War II interrupted his work in Europe he continued these studies in and about San Francisco.

One of the fruits of these labors was the section on *The Early History of Tuberculosis in the State of California*, for the California Tuberculosis Association, in which many interesting and some previously undiscovered facts were brought to light. During these years he served as a member of the Committee on Archives of the National Tuberculosis Association.

In April, 1947, jointly with Dr. Francis Pottenger, he was awarded the first of the Annual Medals of the California Tuberculosis and Health Association for outstanding achievement in the field of tuberculosis.

Doctor Evans died quietly, from a cerebral hemorrhage, on September 5, 1947. Thus ended the full life of an eminent physician—a contemporary of Osler, Koch and that group of pioneer physicians who opened up new eras in the field of tuberculosis.

HAROLD GUYON TRIMBLE

# THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

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**Endobronchial Aspiration.**—Edema of the bronchial mucosa impairs drainage of cavities by narrowing the bronchial lumen and hindering the normal flow of mucus along the bronchial wall. With the view of restoring normal drainage endobronchial application of epinephrine and broncho-aspiration were carried out in 38 cases of inert or ballooned cavities under pneumothorax (the ballooning had most frequently occurred after pneumonolysis). In 33 among the 38 cases bronchoscopic treatment coincided with diminution and disappearance of cavities on X-ray films (86 per cent). Bronchoscopic treatment was started from several months to two years after induction of pneumothorax or pneumonolysis, thus permitting to establish a correlation of cause and effect between therapy and results. The treatment did not provoke any clinically or roentgenologically demonstrable activation of tuberculous lesions. Five cases developed sero-fibrinous pleurisy. The favorable results have been maintained during an observation period of one to eight years. Concerning the technique of endobronchial aspirations, at present widely practiced in France, it is stressed that it is insufficient to place the aspirator into the stem bronchi. The flexible end of the aspirating tube should pass the bronchus of the diseased lobe and then be inserted, if possible, into the intralobar branch corresponding to the cavity. If the localization is uncertain or if the direction of the tube cannot be controlled by direct vision as in the interlobar branches of the right upper lobe, it is recommended to perform several successive aspirations at different angles. The chances

are that one of the attempts will go into the right direction. Aspirations were performed every two weeks. It is claimed that one to eight aspirations were usually sufficient to obtain closure of cavities and conversion of sputum.—*La bronco-aspiration de certaines cavernes pulmonaires tuberculeuses*, J. M. Lemoine & L. Langeard, *Rev. de la tuberc.*, 1947, 11: 179.—(V. Leites)

**Bronchoscopy.**—Chest surveys will reveal many diseases beside pulmonary tuberculosis. Bronchoscopy should be done when there is X-ray and clinical evidence of bronchial obstruction. Visualization of the smaller bronchi and the upper lobe bronchi is impossible but tubercle bacilli and cancer cells can occasionally be aspirated from these bronchi. The bronchoscope may reveal: foreign bodies, sometimes unsuspected; tuberculous bronchitis with lesions varying from the ulcerating or granulomatous stage to healed fibrostenosis (in children it is usually due to penetration of a bronchial lymph node and produces the X-ray findings of a nonopaque foreign body; only by bronchoscopic biopsy can the diagnosis be made); broncholiths (they should be removed bronchoscopically); carcinoma of the bronchi (bronchoscopy with biopsy should be done in all cases where expiration and inspiration films show obstructive emphysema, this condition being suggestive of early carcinoma); sarcoma, Hodgkin's disease, hypernephroma and other neoplasma; fibroma, chondroma, lipoma or papilloma are extremely rare; adenomata; cylindromats; pulmonary abscess; bronchiectasis.—*Bronchoscopy and the Chest Survey*, K. A. Phelps,

*Journal-Lancet*, June, 1947, 57: 246.—  
(O. Pinner)

**Pathogenesis of Tuberculosis.**—Van Beneden summarizes various elements in the pathogenesis of tuberculosis. The importance of the quantitative factor as regards the number of bacilli producing tuberculosis has been well demonstrated. The duration of time intervals between exposures to infection is also of significance. Of previously uninfected animals the youngest are the most susceptible. As to qualitative differences in the virulence of human type tubercle bacilli, responsible for clinical tuberculosis, it has usually been considered slight in France, yet it is known that there are variations. More careful studies should be made regarding the minimal infecting doses for guinea pigs of various strains and the severity of the infection after definite periods of time have elapsed. It is believed that the skin lesions of lupus vulgaris are caused by bacilli of attenuated virulence, perhaps originally virulent when first introduced into the body but which have lost their virulence in the cutaneous tissues. Among well known strains that have lost their virulence in artificial cultivation, BCG and the R strain of Trudeau are mentioned. However, even if all the qualitative differences in virulence of various strains of bacilli were accurately determined and classified, it would still not be possible to establish any definite relationship between them and the degrees of severity of clinical forms of the disease. The variable nature of the human terrain invaded by the germ would remain to be considered. There are two very different types of human terrain in which the bacillus develops, virgin or "physiological" soil in which there has been no previous infection by tubercle bacilli and "specific" or already infected tissue. Infection of the first type is often a silent and mild affair, not resented greatly by the body tissues while the latter is frequently a brutal and violent reaction, a manifestation of specific intolerance. Reference is made to studies of Besançon and De Serbonnes regarding a sort of pulmonary Koch's phenomenon follow-

ing reinfections by the tracheal route. The allergic response as indicated by the tuberculin test is modified by the dosage of bacilli, the technique of application and the quantity of tuberculin. The intracutaneous test is the most sensitive procedure. The Mérieux preparations are especially recommended. There seems to be some relationship between the route of reinfection and the severity of the tuberculin reaction. Allergy shows first of all that the subject is infected. It is no more than a promise of immunity and a second infection may bring in its train all the exaggerated and undesirable manifestations of severe reaction. Certain individuals may be classed as "preferred" victims of tuberculosis. The term allergy has been used too frequently in a limited sense as implying a definite antigen-antibody reaction. For the present it should be reserved as a descriptive term, as an indication of an abnormal or different condition from that originally existing. The modern student of tuberculosis must therefore take into account, not only variations in tubercle bacilli but also of the terrain in which they are sown. The author refers to studies of many French and Belgian workers as well as to his own investigations.—*Quelques vérités premières et quelques inconnues de la phthisiogenèse*, J. Van Beneden, *Rev. belge de la tuberc.*, 1947, 38: 15.—(A. T. Laird)

**Phthisiogenesis.**—The phthisiogenetic rôle of different tuberculous lesions is analyzed from a clinical and roentgenological point of view. The primary pulmonary focus was only exceptionally found responsible for the development of progressive tuberculosis. Among 453 healthy individuals who showed X-ray evidence of a primary complex no signs of progression were noted in an observation period of six to eighteen months. In another group of 271 cases between the ages of 16 and 65 with demonstrable primary foci, a period of observation from three to seven years revealed progression of the pulmonary focus in only one case (0.36 per cent). How often the lymph node component of the primary complex is responsible for phthisiogenesis is believed to

be a question which cannot be answered with precision to-day, since the potential or actual tendency to exacerbation or progression of the lymph node component, with or without calcifications, cannot easily be established by clinical or roentgenological methods. In the cases under investigation calcified hilar lymph nodes were found twice as often as primary pulmonary foci. Their exacerbation was observed only in two instances. The old problem of apical lesions as phthisiogenetic sources is discussed. Analysis of the available material led to the following conclusions: (1) Apical lesions of the Simon type were found extremely seldom between the ages of 1 and 15; 6 cases out of 783 (0.7 per cent). (2) The progression of Simon foci into cavitary phthisis, although possible, is equally rare; 6 cases out of 321 (1.8 per cent). (3) Apical lesions are more often found in adults; 111 cases out of 1,992 (5.6 per cent). They are considered final, late, and mostly inactive phases developing from various forms of tuberculous lesions, of the primary as well as of the reinfection type. (4) According to the author, fresh reinfection lesions of probable exogenous origin, constituting the starting point of progressive phthisis, are observed in all parts of the lung. No connection could be established with the reactivation of old foci of the Ghon or Simon variety. These reinfection lesions showed a tendency to progression which was ten times higher than that of the whole group of apical foci. Thus among 101 cases of soft macro-nodular reinfection lesions having developed in lungs of adults exposed to tuberculosis and with previously negative X-rays, 67.3 per cent showed consecutive progressive changes. In contradistinction, apical foci remained stationary in 84 per cent, regressed in 9.6 per cent, and showed progression in only 6 per cent of cases.—*The Different Age of Reinfection Lesions and Its Role in the Development of Progressive Pulmonary Tuberculosis*, I. E. Kochnova, *Probl. tuberk.*, 1947, No. 2, 20.—(V. Leites)

be health problem No. 1 in Brazil. The campaign so far has been waged almost exclusively along curative lines. The services established on that basis have proved too expensive and inadequate. At the estimated rate of 80,000 deaths a year the provision of beds would require an initial outlay of 800 million cruzeiros (about 50 million dollars). Maintenance would also prove high: 40–44.5 cruzeiros (about \$2.50) per bed-day in 1945 in Rio, as compared to 8.5 cruzeiros (about 50 cents) in the Ferreira Home-Hospital at S. Paulo (a much less pretentious establishment). While many more would be required, only 4,480 beds for tuberculosis patients are either in use or being planned in Brazil as the cost is going up. On the other hand, BCG costs 0.20 cruzeiro (about 1 cent) per dose of vaccine. In the 1942–1944 three-year period 112,588 babies were born in the city of S. Paulo, vaccination of which would have cost 135,000 cruzeiros, or barely as much as the maintenance of 10 sanatorium beds. Thus BCG becomes the choice health weapon when a tuberculosis campaign on an economical basis is planned. The S. Paulo Tuberculosis Division was organized in 1931 and has now a budget of 35 million cruzeiros (about two million dollars), most of which is to be spent on dispensaries and sanatoria. The Federal Tuberculosis Service spent about 50 million cruzeiros (about three million dollars) for sanatoria in 1942–1945. In its new extensive campaign it will employ, however, preventive as well as curative means. BCG vaccinations in the city of S. Paulo in 1942–1945 barely totaled 22,000 and the figures for the interior of the State were much smaller.—*BCG—Recurso sanitario e econômico na luta contra a tuberculose*, B. Pedral Sampaio & A. Nogueira Martins, *An. paulist. de med. e cir.*, January, 1947, 53: 7.—(A. A. Moll)

**Vole Bacillus.**—Wells identified this bacillus in 1937. The disease caused in wild voles is marked by the formation of chalky subcutaneous masses, over which the skin is liable to ulcerate, containing enormous numbers of acid-fast bacilli. The lymph nodes are

BCG in Brazil.—Tuberculosis continues to



extensively involved, with caseation. Lesions sometimes occur in the lungs, liver and spleen. The bacillus has also been recovered from the bank vole, the woodmouse and the shrew. The disease is exceedingly chronic, an advanced stage having little apparent effect on the animal's activity. The life expectancy of the vole is the same whether infected or not. Cannibalism is a possible route of infection. Contaminated water and food also convey the disease. Morphologically, as well as culturally, the vole bacillus is distinct from other types of *M. tuberculosis*. It is indistinguishable serologically from the human and bovine types. Tuberculin prepared from it is about equal to other tuberculins. Tremendous doses of the bacilli are required to kill a guinea pig. The degree of resistance produced by the bacillus in animals is greater than that produced by BCG, as observed by Wells and Griffith. In an experiment by Birkhaug, all controls died in about 200 days, whereas the immunized animals lived from 300 to 600 days. The difference between the vole bacillus and BCG group was not significant. The chances of a spontaneous enhancement of virulence in BCG is thought of as a possibility, whereas this could not occur in the vole bacillus, and the normal host can be used to preserve its present characters. Wells has recently inoculated human subjects with the vole bacillus. A slowly healing ulcer developed at the site of infection. Lymph nodes were not involved. Multiple puncture method was used. It is therefore considered a safe procedure and effective as judged by the acquisition of tuberculin sensitivity.—*The Vole Bacillus*, (Editorial), *Brit. M. J.*, May 31, 1947, 4508: 770.—(R. W. Clarke)

**Dubos' Medium for Isolation of Tubercle Bacilli.**—The present report deals with further experience with these media in the bacteriological diagnosis of tuberculosis. In the previous study several variations of the basic medium as described by Dubos were employed. Since there appeared to be little difference in the results obtained in these various liquid media, further investigation

has been limited to the use of one formula, that most recently described by Dubos, and the solid medium prepared by the addition of agar and ferric ammonium citrate. Since the previous report, 197 specimens have been examined for tubercle bacilli by these methods as well as by guinea pig inoculation. Of these, 28 were positive either by culture or guinea pig, or both. Twenty-three of the 28 were positive by culture as well as by guinea pig. One additional specimen, a gastric aspiration which was positive by culture, did not produce tuberculosis in guinea pigs. The incubation period of these positive specimens ranged from five to twenty-one days, with a mean of 10.6 days, remarkably little time for the bacteriological diagnosis of tuberculosis. The remaining specimens, two sputa and two spinal fluids, were positive by guinea pig only. The results obtained with the small series of specimens when combined with those previously reported show that, of 57 positive specimens examined in fluid media, 50 (87.7 per cent) were positive by culture, while 54 (94.6 per cent) were positive by guinea pig inoculation. Forty-four (88 per cent) of the positive results were obtained within fourteen days of incubation. Too few specimens have been examined on the solid medium to permit analysis. Four strains which failed to grow in broth grew readily on the solid medium. Colony morphology on this medium is strikingly different from that observed on coagulated egg media. Growth occurs as soft, discrete, semitransparent colonies not unlike those of streptococci.—*Further Observations on the Cultivation of Tubercle Bacilli from Pathologic Material in Dubos Media*, G. E. Foley, *J. Lab. & Clin. Med.*, July, 1947, 32: 842.—(F. G. Petrik)

**Survival of Bacilli.**—How are tubercle bacilli modified morphologically, tinctorially and vitally in the various conditions to which they are subjected while en route to the laboratory? Morphological and tinctorial changes were studied by examination every five days of specimens remaining in their original containers. If kept at a temperature

of +7, +22 or +37° C. no significant changes took place after three months in the properties of the bacilli. To study survival of bacilli in sputum, culture and guinea pig inoculations were made daily for ten days, then at ten-day intervals for three months. Bacilli in sputum kept at +7° and +22° C. retained their virulence unchanged up to three months. On the contrary, at +37° C. the bacilli were virulent for only four days; on the fifth day the bacilli were not pathogenic for guinea pigs although an allergic type of sensitivity was produced in the animals. If, however, a drop of penicillin containing 5,000 units was added to 1 cc. of neutralized sputum, the culture or guinea pig inoculation of such a mixture was always positive. Specimens of gastric contents were found to lose gradually their virulence within ten days. From these studies the conclusions are drawn that for direct examination of specimens no special precautions are necessary, whereas if the specimen has to be shipped quite a distance, particularly in warm weather, neutralization and incubation for several hours in the presence of penicillin will not only preserve the virulence of the tubercle bacilli, but will lessen the danger of pyogenic infection to the animals inoculated.—*Persistence des caractères morphologiques et biologiques des bacilles de Koch dans les produits expédiés au laboratoire, F. Tison, Ann. Inst. Pasteur, July, 1947, 73: 684.*—(P. Q. Edwards)

**Bronchial Lavage.**—Bronchial lavage was tried in 260 tuberculosis patients in various stages and modalities. The material obtained proved positive in 29.3 per cent; 26.1 per cent in cultures, 12 per cent by inoculation in the guinea pig and 8.0 per cent by direct examination, some specimens by more than one method. The rate of positivity varied from 100 per cent in 4 ulcerated fibro-exudative cases to 8.6 per cent in 46 cases under pneumothorax treatment. Out of 155 fibrotic cases 20 per cent were found positive. Bronchial lavage should be repeated at least three times. The method is much easier than gastric washing and less bothersome for the

patient, the indications for both methods being identical. Hemoptysis, heart failure, respiratory difficulty and asthma cases should be excluded. Allergic symptoms following the test develop in about 31 per cent of patients, usually in a very mild form and headache being the most common. Deep breathing is emphasized to patients liable or about to cough. A most detailed description of the technique is given. The writer agrees with Fontes Magarão that bronchial lavage is the most appropriate name for the procedure.—*A lavagem brônquica no diagnóstico da tuberculose, J. Estevão Correia, Rev. méd. munic. (Rio de Janeiro), October-December, 1946, 9: 105.*—(A. A. Moll)

**Serum Changes in Chronic Diseases.**—By means of the electrophoresis technique, the serum protein, lipid and polysaccharide patterns were studied in cases of minimal, moderately advanced and far advanced active pulmonary tuberculosis, in cases of minimal and moderately advanced pulmonary tuberculosis of questionable clinical significance, in cases of sarcoidosis, in cases of various carcinomata and in a few cases of diabetes mellitus. In early active tuberculosis, slight rises occur in the gamma globulin fraction, which presumably represents antibody formation, and may have prognostic significance. In advanced stages, all the globulin fractions, especially the alpha 2 globulin, as well as polysaccharide, increase, presumably representing tissue destruction; however, the mean total protein does not change. As the disease heals, there is a return to the normal serum picture. In sarcoidosis, there is an increase in total protein and in gamma globulin, and only a moderate rise in polysaccharide (possibly emphasizing the nondestructive nature of the disease). In carcinoma there is decrease of total protein, and a large increase in alpha 2 globulin and in polysaccharide—again possibly indicative of tissue destruction. There are definite differences in the analytical patterns of the three diseases which might have value in differential diagnosis.—*Varia-*

*tion in Protein and Polysaccharide Content of Sera in the Chronic Diseases, Tuberculosis, Sarcoidosis, and Carcinoma, Florence B. Seibert, Mabel V. Seibert, A. Jane Atno & H. W. Campbell, J. Clin. Investigation, January, 1947, 26: 90.—(A. A. Cohen)*

**Paraspecific Reactions.**—The pathology of so-called paraspecific reactions was studied in primary tuberculosis of adolescents and adults. The early involvement of vessels at the site of infection was noted, which permits to assume the development of bacillemia as a constant feature in the early stage of primary tuberculosis. Bacillemia is considered one of the main factors in the causation of the specific sensitization of the organism and of hyperergic tissue reactions. In the course of these immunological changes during primary tuberculosis specific and paraspecific processes take place in many organs, the best known manifestations of the latter reaction being erythema nodosum, phlyctenulae and rheumatic involvement of the Poncet type. The authors studied paraspecific reactions in internal organs. Their main characteristics were found to be as follows: (1) Diffuse accumulation of macrophages in the capsule and interstitial tissue of inner organs, in serous membranes and in the myocardium. (2) The infiltration with these cellular elements occurred also in nodular form and was found mainly in the perivascular tissue of the myocardium. (3) Diffuse or nodular infiltrations consisting of histiocytes and lymphocytes, mainly observed in the capsule and stroma of lungs, kidneys, liver, synovial membranes and heart. (4) Nonspecific inflammatory changes in the vascular system involving small and large arteries and veins. (5) Fibrinoid necrosis in the lungs and elsewhere. Tubercle bacilli were never demonstrable at the site of these paraspecific reactions. However, a correlation was noted between the extent of the paraspecific tissue changes and the bacillary content of the primary focus. The pathogenesis is considered to be an allergic mesenchymal re-

action to bacillary toxins. Resemblances are seen between these hyperergic tissue reactions and those observed in rheumatic fever.—*The Morphology of Paraspecific Tissue Reactions in Tuberculosis, A. I. Strukov, Probl. tuberk., 1947, No. 2, 57.—(V. Leites)*

**Miliary Tuberculosis with Heart Involvement.**—In a case of acute miliary tuberculosis in a 22-year-old man, necropsy revealed both in the heart muscle and the endocardium several lesions. Some were clearly tuberculous and others of a rheumatic type; the etiology seemed uncertain, although the histological picture confirmed their tuberculous nature. It was not determined whether the endocardium or the heart muscle had been first attacked. Valvular lesions seem most uncommon in tuberculosis. In about 100 cases of acute miliary tuberculosis this was the only one in which valvular or nodular lesions were detected in the heart muscle.—*Lesões tuberculosas cardíacas em tuberculose generalizada aguda de adulto, C. Mignone & F. Gikovate, Cltn. tisiol. (Rio de Janeiro), October-December, 1946, 1: 541.—(A. A. Moll)*

**Bone Tuberculosis.**—The common conception that the sedimentation rate is increased in tuberculosis of the bone proves to be erroneous in the 6 cases described in the present paper. None of these patients had clinical or X-ray evidence of pulmonary tuberculosis. They were all adult patients without draining sinuses and all but one had proved tuberculous lesions of the bones. All had normal sedimentation rates. Detailed histories are given, with X-ray reproductions, to substantiate the above statement regarding the sedimentation rate as a diagnostic criterium.—*Low Sedimentation Rate Observed in Osseous Tuberculosis, K. Yanagisawa & D. Bosworth, Quart. Bull. Sea View Hosp., January, 1947, 9: 21.—(P. Q. Edwards)*

**Tuberculosis of Prostate.**—Hematogenous dissemination of tuberculosis to the male

urogenital system almost invariably produces involvement of the prostate, which appears to be the site of predilection for tuberculous infection. Secondary to tuberculosis of the prostate, the urinary bladder becomes involved in the tuberculous process by direct extension from the prostatic urethra. Ascending infection to the ureter or kidney is very rare, if it occurs. Caseation and liquefaction of one or more foci of infection in the prostate lead to coalescing of the lesions with eventual rupture into the prostatic urethra or rectum, producing a cavity in the gland and a fistulous tract. Involvement of the seminal vesicles and epididymis usually results from intracanalicular extension from the prostate. Healing may take place in the gland with formation of calcifications encased in a fibrous capsule. As the process continues contraction of the tissues causes shrinkage of the gland which, on palpation, may simulate carcinoma. Demonstration of calcium roentgenographically will clarify the diagnosis. Symptoms of tuberculous prostatitis are obscure and multiple. Induration and irregularity of the gland, enlargement, discrete nodulations and occasionally fluctuation from liquefaction of a focus should suggest tuberculosis. Red cells in the urine and bacilluria are usually present but of inconclusive diagnostic use in the presence of tuberculosis of the kidney, epididymis or seminal vesicles. Asymmetry between the two lateral lobes on rectal examination, fluctuant sensation in one lateral lobe, some tenderness of the prostate and occasionally a prostate which is smaller than normal are additional findings characteristic of tuberculosis of the prostate. Transurethral resection is contraindicated in tuberculous involvement of the prostate for either diagnostic biopsy or removal of the gland because of the danger of sinus formation, perforation, fistula or even spread of the disease. Radical perineal prostatectomy (Young's procedure) is preferred rather than transurethral resection or the suprapubic approach since both latter methods fail to completely remove the tuberculous tissue and

thereby invite the complications cited above. —*Tuberculosis of the Prostate*, E. Muehsam, *Quart. Bull. Sea View Hosp.*, January, 1947, 9: 25.—(P. Q. Edwards)

**Ocular Tuberculosis vs. Jensen Retinitis.**—Four cases of Jensen's retinitis, an acute localized lesion of the retina producing persistent scotoma are reported. In 2 of them the tuberculin skin test was negative and the lesion is ascribed rather to syphilis. It is concluded that Jensen's retinitis is not necessarily a form of tuberculosis although it may in some cases be associated with and perhaps due to infection by Koch's bacilli.—*Apropos des tuberculoses oculaires; la rétinite de Jensen*, G. Renard, *Presse méd.*, June 4, 1947, 33: 376.—(E. Bogen)

**Sarcoidosis.**—Between March 1, 1943 and March 31, 1944, all recruits entering the Swiss army were subjected to routine fluoroscopy. Of 516,879 men fluoroscoped, 115 were referred for detailed study with the provisional diagnosis of sarcoidosis. Of these, 67, or 0.13 per thousand, were definitely diagnosed after detailed investigation. Since the means of diagnosis was invariably directed towards the chest, all cases had either involvement of the lungs and or hilar lymph nodes. The diagnosed cases frequently showed involvement of peripheral lymph nodes and spleen on physical examination, whereas skin and skeletal lesions were rare. Because of the uncertain relationship of sarcoidosis to tuberculosis, it was felt advisable to give all definitely diagnosed cases a medical discharge. The series herein reported includes many persons who had done previous military service, but a causal connection between service and disease was denied in almost every case by the compensation board. The question of compensation was not often raised since the greatest number of cases were completely asymptomatic and able to work a full day. Exclusion from military service is in the nature of a "prophylactic" measure.—*Morbus Besnier-Boeck-Schaumann und Armeedurch-*

leuchtung, G. Schönholzer, *Schweiz. med. Wchnschr.*, May 31, 1947, 77: 585.—(H. Marcus)

**Familial Sarcoidosis.**—Sarcoidosis occurred in siblings of two unrelated families. In one family at least 2 of the 3 siblings were affected, and in the other a diagnosis was established for 3 siblings and was probable or possible for at least 3 others of a total of 10 siblings. Cutaneous lesions were found in only 2 of the patients discussed. Active tuberculosis ultimately developed in 2 patients. (Authors' Summary.)—*Sarcoidosis in Siblings*, R. C. V. Robinson & R. D. Hahn, *Arch. Int. Med.*, August, 1947, 80: 249.—(G. C. Leiner)

**Atypical Pneumonia.**—In view of the current interest in the disease known as primary atypical pneumonia, the question is raised: Is it a disease, a syndrome or a fiction? Review of clinical findings reveals that the onset is characterized by malaise, chilliness, fever and rhinopharyngitis. Penicillin and sulfonamides are ineffective in altering the expected course of gradual abatement of the cough and fever within several weeks. Radiological signs of bronchopneumonitis are transient and probably dependent upon bronchial infection with obstruction from secretions, causing pneumonitis in the distal parenchymal segments. Initial leucopenia succeeded by mild leucocytosis is present in many illnesses, as is the demonstration of cold agglutinins, which are variable in appearance. Pathological studies are not available as the disease is rarely fatal; etiology is still unknown. The conclusion, therefore, seems justified, at the present time, that primary atypical pneumonia is not a disease; it is a syndrome, similar to Loeffler's syndrome, if cold agglutinins are present; in all other cases it is a fiction.—*La pneumonie atypique primitive*, (Editorial), *Rev. de la tuberc.*, 1947, 11: 186.—(P. Q. Edwards)

**Pneumonia at Camp Gruber.**—This article is a supplement to the article by J. C. Cain, E. J. Devins and J. E. Downing: "An Un-

usual Pulmonary Disease" in *Arch. Int. Med.*, June, 1947, 79: 626. The conclusion is as follows: "Studies on specimens from patients with pneumonia occurring at Camp Gruber, Oklahoma, have failed to identify a causative agent. Attempts to reproduce the disease in animals were unsuccessful. Although *C. albicans* was isolated in 10 of 17 patients ill with pneumonia, the rôle of this organism is questionable because of the lack of supportive evidence."—*Studies on the Causation of an Unusual Pulmonary Disease at Camp Gruber, Oklahoma, Commission on Acute Respiratory Diseases, in collaboration with W. A. Mickle, Jr.*, *Arch. Int. Med.*, August, 1947, 80: 203.—(G. C. Leiner)

**Loeffler's Syndrome.**—A case of lung infiltration associated with eosinophilia and asymptomatic chronic amebiasis is reported.—*Loeffler's Syndrome*, Capt. A. W. Pearlman, *Am. J. Roentgenol.*, July, 1947, 58: 75.—(J. E. Farber)

**Residual Lung Abscess.**—Following incision and drainage for acute lung abscess residual cavities often remain. These are usually complicated by broncho-cutaneous fistulae and by bronchiectatic changes in the surrounding lung parenchyma. Because obliteration of the pleural space is a condition of the original incision and drainage operation it was anticipated that lobectomy several years later would be exceedingly difficult. The author has successfully operated on 3 patients in whom this was not the case. Adhesions were present only immediately overlying the diseased lung tissue and surrounding the fistula. The remainder of the lobe could be separated from the parietal pleura with ease, and with only slightly more difficulty from the remaining lobe. The operation is carried out under local anesthesia. The fistula is excised and the regenerated bone removed. Because the pathological process is always located peripherally, individual dissection and ligation of the root structures is not necessary. The wound is closed tightly in layers, and intercostal suction drainage is

instituted immediately to encourage expansion of the remaining lobe. The drain is shortened gradually and completely removed after several weeks. One of the 3 patients had been in poor health due to residual abscess and fistula for five years prior to lobectomy, and a complete cure was achieved.—*Die Behandlung der Lungenabszessresthöhlen mit Hilfe der Lobektomie*, A. Brunner, Schweiz. med. Wchnschr., June 14, 1947, 77: 630.—(H. Marcus)

**Pneumonia in Varicella.**—A 32-year-old female patient with chickenpox and pneumonia was observed. The patient died on the eleventh day of the disease. The autopsy revealed extensive consolidation of all lung lobes. The consolidation consisted of small nodules about 5 mm. in diameter and frequently coalescent. Many of the nodules were hemorrhagic. Attempts at virus transfer were unsuccessful.—*Pneumonia Associated with Varicella: Review of the Literature and Report of a Fatal Case with Autopsy*, W. D. Claudy, Arch. Int. Med., August, 1947, 80: 185.—(G. C. Leiner)

**Compensation for Silicosis in Belgium.**—A series of royal decrees has authorized compensation for disabled silicotics since 1927. The one which became effective in 1937 contained conditions which it has proved somewhat difficult to meet. In order to secure compensation, the workman must have worked at least three years in a dust laden environment and have become permanently incapacitated. In addition, his sputum must show phagocytes containing silica particles, and an X-ray film of his chest must be interpreted as showing the so-called pseudo-tumor aspect considered characteristic of the third stage. Experience has shown that while phagocytes containing dust particles are often present in the alveoli and pulmonary lymphatics, they are rarely expectorated by the patient. The pseudo-tumor appearance in the X-ray film has been found to be compatible with working ability in certain cases where it is present, and absent in others where there is total disability. In

actual experience it has been considered adequate evidence of disability if the X-ray shows other indications of severe silicosis, accompanied, or not, by signs of pulmonary tuberculosis. The author feels that the laws should be revised, after thorough study of the subject by the medical profession. He, as medical director of the Sanatorium Brugman at Alsenberg, was invited to present this paper before the Society for the Scientific Study of Tuberculosis and Pneumology. As he says, it is a résumé and contains nothing especially original. However, he brings out some interesting phases of the subject. Silicosis, he states, is due to a pathological condition of the lung resulting from the inhalation of particles of free silica. It is frequently complicated by pulmonary tuberculosis and often confused with it. It develops in three stages. The first is characterized by a special type of fibrosis consisting of a maze of fine fibres, the second by the primary silicotic nodule, and the third by pseudo-tumor formations. The first two stages can be detected only in X-ray films of good quality. The lack of symptoms has often been responsible for the failure to secure X-ray films in the first stage, when the characteristic changes were already present. Accordingly it is advisable to have periodic X-ray films taken of all exposed workers. The fibrosis of the first stage presents a characteristic reticular appearance. It results from the partial filling of the lymphatic vessels and spaces with irritating dust particles, which brings about a peribronchitis producing an outline of the pulmonary framework on which there appear here and there thickened granular masses of no special significance which are generally thought to be due to superposition of crossing fibrous tracts at different levels. The solubility of the silica, which in fact is very slight, is an explanation of its toxic action, which is also favored by the lymphatic stasis. The fibrosis seen in the film often outlines with startling precision the two routes of the lymph currents which carry the silica either to the hilar nodes or the subpleural spaces. This characteristic X-ray finding in the first stage may appear very

quickly in some workers exposed to an excess of silica dust. On the other hand, there are a considerable number of older workers who have observed no hygienic precautions and yet do not show it. The silicotic nodule of the second stage has been considered by some, notably Policard, as an indication of the tuberculous origin of silicosis. Gardner, however, has shown that it may be produced by the inhalation of silica dust alone, especially of fine particles between 0.2 and 10 micra in diameter. Below 0.2 micra, the author considers, we enter the domain of aerosols which seem to be inoffensive. Anything that causes dyspnea he considers a predisposing factor in silicosis, such as atmosphere surcharged with carbon dioxide. Particles small enough to remain in suspension, in the so-called "live" state, are particularly harmful, hence the usefulness of ventilation. The Antituberculosis League is making an effort to secure a relaxation of the severe restrictions on double food rations for the benefit of workers in silica laden dusts. Coal miners rarely develop silicosis though they may have pneumoconiosis.—*Silicose, tuberculose, anthracose, J. Andre, Rev. belge de la tuberc., 1947, 38: 89.*—(A. T. Laird)

**Beryllium Poisoning.**—There are two types of reaction which apparently can result from exposure to beryllium-containing compounds: an *acute* pneumonitis, which may either be fatal or clear without residue; and a *chronic* condition which does not develop until a few months or years after exposure, and consists of sarcoid-like lesions in the lungs, lymph nodes, skin and other tissues with cachexia, hypoxemia and right-heart strain, irreversible and often fatal. This latter entity was first reported in the fall of 1946 by Gardner and by Hardy; most of the cases have been found in a group of workers in a single fluorescent-lamp plant, but others have been found in the numerous industries using some form of beryllium. There are two odd features in these lesions: appreciable amounts of beryllium cannot be recovered from the tissues; and a nonpathogenic, irregularly acid-fast bacillus is

sometimes found in the sputum, tissues or blood-stream. A typical case with unusual features is described. The symptoms began abruptly four years after exposure to a beryllium compound, and the lesions became fully developed in the lungs, nodes and skin within a few months. Typical lesions were found in a biopsy of the skin, but no acid-fast bacilli were found in the sputum. Signs of involvement of other organs included a serious cardiac irritation, cerebral irritation with elevation of the spinal fluid pressure, and sporadic renal irritation. Typical acute secondary bronchial and lung infections repeatedly occurred. In place of the common hypotension, episodes of increasing arterial hypertension occurred. A failure of the right side of the heart, with early decompensation, began. BAL was used for the first time in such a case, but it produced mild toxemia, no improvement and no excretion of beryllium. It should be tried on other cases. Streptomycin also deserves a further trial; it could not be used in this case, but the one case previously reported showed temporary improvement during a brief use of the drug. All employees in the numerous industries using beryllium should be protected from contact with the compounds in the form of fumes, dust and liquid suspensions; they should be recurrently examined by some X-ray method; and physicians in areas remote from sources of exposure should be alert for transient cases.—*Beryllium Granulomatosis, alias Miliary Sarcoid, Salem Sarcoid, Miliary Sarcoidosis, Chronic Beryllium Poisoning, or Delayed Chemical Pneumonitis, J. Pyre & W. H. Oatway, Jr., Arizona Med., September, 1947, 4: 21.*—(W. H. Oatway, Jr.)

**Carcinoma of Lung.**—The recent increase in the frequency of carcinoma of the lung and the development of a curative procedure, pneumonectomy, have accentuated the importance of early diagnosis. However, the onset is insidious, the symptoms are often deceptive, and the physical signs, if at all present, may imitate other pulmonary diseases and vice versa. Aside from exploratory thoracotomy with biopsy which, perhaps, should be used

more frequently, the best method is bronchoscopy with biopsy; but this also has its limitations and permits of no more than 50 per cent positive diagnoses. First evidences of a bronchogenic tumor must be obtained by X-ray examination. At routine surveys early lesions will frequently be discovered. Examination on inspiration and expiration and in a variety of positions of the patient are important for the discovery of atelectasis, emphysema or tumor formation and for the demonstration of the anatomical location. Tomography and bronchography will in many instances show the exact site of the bronchial obstruction and of the tumor and even the tumor mass itself. The X-ray findings are most variable. The roentgenological pictures of several types of tumors are described, and the differential diagnosis from inflammatory lesions, unresolved pneumonia, pneumonic abscesses, fungus infections, is outlined. More important are the findings of bronchial obstruction caused by tumor within the bronchus and of its sequelae as band-like atelectasis; massive atelectasis with retraction of the interlobar fissures, elevation of the diaphragm and retraction of the mediastinum toward the side of the lesion; the appearance of a drowned lung due to intrabronchial retention of large quantities of fluid and to excessive afflux of blood into the atelectatic lung; or emphysema, occurring with incomplete obstruction. Tomography is especially helpful in the diagnosis of benign tumors but also malignancies can be diagnosed by this method even without bronchoscopic procedures. Bronchoscopically the tumors of the bronchi produce fairly characteristic types of obstruction, for example a cap-shaped defect in the lumen, a marginal, ragged defect within the contrast medium similar to that seen in stomach carcinoma or, more commonly, the "rat-tail" deformity in which the terminal bronchus is frayed out, elongated and extremely narrowed. A rounded or lobulated mass in the mediastinum on the side of a lung density should always suggest a tumor rather than an inflammatory process.—*The Early Diagnosis of Carcinoma of the Lung*, L. G.

Rigler, *Journal-Lancet*, June, 1947, 57: 243.—(O. Pinner)

**Planigraphy in Lung Carcinoma.**—Planar roentgenography is of diagnostic value in lung cancer. Bronchial tumors, bronchial obstruction and lung abscess may be visualized by this method. This procedure, however, does not differentiate between bronchial obstruction caused by tumor and obstruction caused by foreign body, pleural effusion, pneumonic consolidation or other lesions.—*Planigraphy. III. An Evaluation of the Method in the Diagnosis of Cancer of the Lower Respiratory Tract*, J. R. Andrews & R. O. Turek, *Am. J. Roentgenol.*, August, 1947, 58: 173.—(J. E. Farber)

**Gelatinous Carcinoma of Bronchus.**—The main feature of this case of cancer of the lungs was the profuse and persistent bronchial discharge (over a quart a day). This confused for a long time the diagnosis. This was first tentatively made on the basis of the X-ray picture and after ruling out syphilis, tuberculosis, bronchiectasis and atelectasis secondary to bronchial cancer. The conclusion was confirmed in life through biopsy. The patient died within four months from a cachectic condition. An X-ray film taken one month before death showed progress of the disease on both sides of the chest. The literature discloses 2 previous similar cases (Williams' in 1841 and Bliss's in 1936). In both the diagnosis was made postmortem.—*Cancer gelatinoso del pulmón en forma broncorreica*, J. C. Rey & P. Rubinstein, *Presna méd. argent.*, May 16, 1947, 34: 896.—(A. A. Moll)

**Pulmonary Hamartoma.**—A postmortem in a 49-year-old miner with a pulmonary process revealed a bronchopulmonary hamartoma associated with purulent discharge and minimal residual tuberculosis. This is the first case of its type in a series of 1,050 necropsies in the Tornú Hospital in Buenos Aires. Because of their small size, these are probably overlooked but might be detected oftener if routine histological examinations



were made in all nodules in the lung. In Argentina 2 cases were reported by Cid in 1940 and 2 others by Bianchi and Etchegoyen in 1944. Both case reports were postmortem findings.—*Hemarcionoma brónquico intrapulmonar*, R. I. Laticinda, *Rev. Assoc. méd. argent.*, May 15, 1947, 61: 292.—(A. A. Moll)

**Meigs' Syndrome.**—This paper presents an analysis of 37 cases of hydrothorax with benign ovarian tumors and ascites in addition to reporting the second instance of the finding of a pseudomucinous cystadenoma of the ovary. In analyzing the 38 cases listed, we find that the tumors most frequently occur during the menopause or just before. In all of the cases, cultures made of the fluid were sterile, and the fluid was a transudate devoid of malignant cells. There seems to be no relationship between the amount of hydroperitoneum and hydrothorax. Neither does there seem to be any connection between the location of the tumor and the side of the hydrothorax. All combinations are present, such as: right ovarian tumor with left hydrothorax, left ovarian tumor with right hydrothorax, bilateral tumors with right, left and bilateral hydrothorax. Up to the present time, no cause for the syndrome has been agreed upon. It has been suggested that there may be a lack of right lung drainage by the azygos vein, but this does not explain left hydrothorax. A more recent theory deals with the induction of a histamine toxicosis or anaphylactic shock by the repeated peritoneal trauma of the ovarian tumor and the subsequent production of transudates. Meigs showed the hydrothorax and ascites to be of almost identical protein composition and established some form of communication between the two by showing that particulate carbon, after being injected into the abdomen, almost immediately appeared in the plural fluid but not in the blood-stream. Surgical removal of the ovarian tumor always results in the disappearance of the pleural and abdominal fluid.—*Pleurisy with Effusion Associated with Pseudomucinous Cystadenoma (Meigs Syndrome)*, E. D. Nora & R. M. Davison, *Dis. of Chest*,

September-October, 1947, 13: 423.—(E. A. Rouff)

**Metastases in Ribs.**—Primary carcinoma of the lung invades the bony thorax in about 5 to 10 per cent of the cases. Squamous cell carcinoma of the peripheral bronchi is the most common source of such metastases; the growth is invasive, but it occurs late and grows slowly. Extension indicates an advanced lesion, *but not a hopeless one*. Excision of a wide area ("block-excision") of soft and bony tissues usually will remove the neoplasm. It has been reported that metastasis to regional nodes does not often occur. In the present series of 88 cases of pulmonary carcinoma, 17 were eligible for resection, and 7 had metastases. The diagnosis was usually late, since the lung symptoms were scanty and pain eventually led to examination. Radiographic examination is the best method for diagnosis of the lung lesion; an overexposed film is the means of diagnosing rib involvement; bronchoscopy is of no value for these peripheral lesions; exploratory thoracotomy is the method of choice for tissue diagnosis and operability; and block-excision of the chest wall is the correct operative technique. Involvement of mediastinal nerves and vertebrae contraindicates curative surgical attempts, but spread to contiguous extrinsic chest muscles does not. Six of the 7 cases in this series had lesions of the ribs, and the seventh had extension only to the soft tissues. Six of the patients came to surgery; 5 had a block-excision of the chest wall. Four of those with block-excisions had a pneumonectomy; one had a palliative lobectomy, due to the presence of vertebral metastasis. There was one operative death, probably from cerebral asphyxia due to vaso-spasm after injury to the sympathetic trunks. The lobectomy case lived for eleven months after operation. The remaining 3 patients are living and well, one at six years, one at two years, and one at five months after operation. Invasion of ribs by primary carcinoma of the lungs is not uncommon, and is often amenable to radical surgery.—*Primary Carcinoma of the Lung, with Invasion of*

*the Ribs, F. P. Coleman, Ann. Surg., August, 1947, 126: 156.*—(W. H. Oatway, Jr.)

**Roentgenogram of Thorax.**—During 1945, 68 cases of cardiac tumors of the stomach were seen at the Mayo Clinic. In 35 cases the chest roentgenogram showed a tissue mass which projected from the lesser curvature side into the gas bubble of the stomach. The importance of observing the air-filled upper segment of the stomach is stressed because many diagnoses can be made or suspected without, or before, the use of radiopaque media.—*Roentgenograms of Thorax That Suggest Carcinoma of Stomach, B. R. Kirklin & Eva L. Gilbertson, J. A. M. A., August 9, 1947, 134: 1228.*—(H. Abeles)

**Intrathoracic Lipomata.**—A total of 39 cases of intrathoracic lipomata have been reported. Classification according to position includes three types: (1) lipoma lying entirely within thoracic cage, 23 cases; (2) dumb-bell type, with a portion lying inside the thorax and extending through an intercostal space to a portion lying outside of the thoracic cage, 9 cases; and (3) mediastinal lipomata, extending into root of neck, 7 cases. Type one was found 14 times in males and 8 in females. Ages ranged from 4 to 65 years. Eight were on the right side, 8 on the left, 4 in the anterior mediastinum, one in the posterior mediastinum and 2 unknown. Nine cases were treated by operation with 6 recoveries and 3 recurrences. The largest tumor weighed 8 kg. The age distribution in type 2 was from one to 56 years. Four were on the left and 3 on the right. All patients were operated upon with 4 deaths and 5 recoveries. The largest tumor weighed 500 g. In type 3, the age range was 6 to 50 years. All tumors arose centrally and extended to the right in 3 cases and to the left in one. There were 6 operations with 5 recoveries and one death. The largest tumor weighed 3.1 kg. The predominant symptom was progressive dyspnea. In other cases, cough, hoarseness, cyanosis and edema of the upper extremities were found. The physical findings often suggest

pleural effusion but on X-ray films the lesions are more circumscribed. All the tumors are extrapleural and arise from fat.—*Intrathoracic Lipomata, J. Smart & V. C. Thompson, Thorax, September, 1947, 2: 163.*—(A. G. Cohen)

**Mediastinal Cysts and Tumors.**—The authors review both the cases reported in the literature and their own cases at Fitzsimmons General Hospital. (A) *Congenital cysts:* 1, 2, 3) Epidermoid cysts, dermoid cysts and teratomata: There are two theories of pathogenesis, monogerminal and bigerminal. The monogerminal theory is favored but not proved; the cysts are regarded as abnormalities of the third and fourth branchial arches. A total of 245 cases have been reported until 1945. The cysts are important because they may: (1) cause pressure symptoms as they increase in size, (2) become secondarily infected, (3) rupture into a bronchus, blood vessel or pleura or (4) undergo malignant degeneration. Treatment is surgical excision. The differential diagnosis among the three types is made grossly. Epidermoid cysts are lined by squamous epithelium only. Dermoid cysts are lined by squamous epithelium with added elements of skin derivatives (sebaceous glands, hair, teeth) in the wall. Teratomata contain elements of all three primitive layers so that epithelial derivatives, gut, respiratory tissue, muscle, bone, cartilage, lymphoid tissue, brain and thyroid may be found. The authors report one case of dermoid cyst and 3 of teratomata. 4) Pericardial celomic cysts: These are lined by thin mesothelium. They originate as a result of failure of one of the primitive pericardial lecunae to merge with others. They are known also as "spring water" cysts. The characteristics are: (1) thin-walled cyst, (2) clear fluid content and (3) lining membrane of endo- or mesothelium. The literature includes 7 cases; the authors report 8 cases. 5) Bronchial cysts: These are lined by ciliated columnar epithelium. They are supposed to arise by the pinching off of a bit of tracheal bud. Cartilage and smooth muscle bundles are frequently present

in their walls. The literature contains reports of 35 cases and the authors report 5.

6) Esophageal and gastroenteric cysts: These are remnants of embryonal gastro-intestinal tract tissues. If the cyst is within the wall of the esophagus, it is esophageal; otherwise it is bronchial. Both are lined by ciliated columnar epithelium. Gastroenteric cysts resemble embryonal stomach or intestinal tissue. The literature contains 25 cases and the authors report one.

7) Cystic lymphangiomas or hygromata: These are rare in the mediastinum. They are multiloculated, have an endothelial lining with smooth muscle and lymphocytes in the wall and contain fluid. There are reports of 8 cases in the literature.

(B) *Acquired cysts*: These include echinococcus cysts, broken down neoplasms and degenerated hematomata. They are all rare in the mediastinum.

(C) *Connective tissue tumors*: 1) Fibromata: There are 32 cases in the literature. They cause pressure symptoms. 2) Lipomata: Most intrathoracic lipomata arise in the mediastinum. They cause pressure symptoms. The literature contains reports of 36 cases and the authors report 3. 3) Leiomyomata: It is important to remove these because they may become sarcomatous. They are generally extramural to the esophagus. 4) Xanthomata: These are considered benign but may become malignant. There are 10 reported cases in the literature. 5, 6, 7) Chondromata, chondromyxomata and chondromyxosarcomata: These originate from cartilage located in the sternum, costal cartilages, articular surface of the spine or costo-vertebral junctions. They may become very large and malignant. The literature contains 4 case reports.

(D) *Neurogenic tumors*: 1) Neurofibromata: These arise from perineural or endoneural fibrous tissue. The literature contains reports of 21 cases of neurofibromata and 19 cases of neurinomata (Schwannomata); the authors report 3 cases of the former and one of the latter. 2) Ganglioneuromata: These contain completely differentiated tissue with very slight tendency to malignancy. The literature contains re-

ports of 68 cases, mostly in children. The authors report 2 cases. 3, 4) Neuroblastomata, neuroepitheliomata: These are more malignant types. (E) *Primary tumors of thymus*: 1) Benign thymomata: A possible relationship to myasthenia gravis is discussed. 2) Malignant thymomata: These are either lymphosarcomata or carcinomata. They may be encapsulated or may invade or metastasize. 3) Thymic cysts: These are rare in adults. The authors report one case. (F) *Primary tumors of lymph nodes*: 1) Lymphosarcoma. 2) Hodgkins disease. 3) Sarcoidosis. 4) Endotheliomata. (G) *Primary and secondary sarcomata*: All primary connective tissue tumors may become sarcomatous. They cannot be differentiated from benign tumors preoperatively. Secondary sarcomata are very rare. (H) *Primary and secondary carcinomata*: Primary carcinomata arise in the thymus but primary sarcomata are four times as common. Secondary carcinomata originate from the lungs, esophagus and breast. (I) *Intrathoracic goiter*.—*Mediastinal Cysts and Tumors*, M. L. Bradford, H. W. Mahon & J. B. Grow, *Surg., Gynec. & Obst.*, October, 1947, 85: 647.—(A. G. Cohen)

**Carcinoma of Trachea.**—Up to December, 1945, a total of 507 cases of tumors of the trachea had been reported in the literature. These included 253 simple tumors, 187 carcinomata, 38 other types of malignant tumors and 29 tumors of unknown nature. Thus carcinomata comprised 37 per cent of the total and 83 per cent of all malignant tumors. Precise histological data were available in 120 carcinoma cases; of these, 50 were squamous cell, 14 basal cell and 56 adenocarcinoma. The earliest complaints are dryness and tickling of the throat accompanied by an irritating cough. Dyspnea is the most prominent symptom; it is influenced by posture. In posterior wall tumors there is loss of weight, especially if the esophagus is invaded. Hoarseness and aphonia may be present. Few symptoms are due to distant metastases. On examination, wasting may be present. Dyspnea, associated with stridor, is evident;

the stridor is best heard at the mouth. Slight pressure over the trachea may give complete obstruction. Fetor oris and cervical adenopathy may be present. There usually is no clubbing of the fingers. X-ray films are normal unless there is secondary pulmonary collapse or infection. Several correct diagnoses have been made by direct X-ray examination of the trachea, particularly in lateral views. Tomography and tracheography are valuable. Precise diagnosis is made by endoscopy and biopsy. Histologically there are several types: (1) Primary carcinoma arising from cells normally present in the trachea: a) squamous cell, b) basal cell and c) adenocarcinoma. (2) Primary carcinoma arising from rests in the trachea of the epithelium of other structures, such as esophagus, thyroid and remnants of branchial clefts. The most frequent type of spread is directly to the esophagus. Metastases are most common in the squamous cell type and may be found in any part of the body; frequency in the order named is to the peritracheal, cervical and tracheobronchial lymph nodes, lungs, liver, supraclavicular and axillary nodes, esophagus, spleen, pancreas, kidneys and skeletal structures. The most common primary site is the posterior wall of the lower third of the trachea; the upper third is least frequently involved. The condition is more common in males. Squamous cell neoplasms are less amenable to treatment than adenocarcinomata. A few successful resections of the trachea have been recorded. In other cases, treatment has consisted of surgical diathermy, insertion of radon seeds and deep X-ray therapy.—*Primary Carcinoma of the Trachea*, P. Ellman & H. Whittaker, *Thorax*, September, 1947, 2: 153.—(A. G. Cohen)

**Thymectomy in Myasthenia Gravis.**—This was almost always a fatal disease before treatment with prostigmine was introduced. An accurate diagnosis of myasthenia gravis must be made before surgical treatment is considered. As a rule, the diagnosis can be made easily but the disability has too often been wrongly attributed to some serious neuro-

logic disorder considered incurable. There are three identifying features of this disease. It is selective, it is visible and it is variable. It almost always begins in the muscles controlling the movements of the eyeballs and the muscles concerned with speech, swallowing and mastication; general muscular weakness develops as the disorder progresses. The change in muscular function tends to appear with repeated effort and to decrease or disappear with rest. There is almost immediate relief lasting for several hours following the injection of prostigmine. After the diagnosis has been established, medical treatment should always be carried on for a trial period of at least six months. This consists of ephedrine, 25 mg., twice daily, and prostigmine, in 15 mg. tablets, numbering two to twenty-four daily as needed to secure results. Potassium chloride and guanidine are of uncertain benefit. Continued disability after six months of medical treatment is the essential situation in which surgical treatment should be considered. Thymectomy is a surgical procedure of great magnitude and the very nature of the illness makes operation of any kind on patients with myasthenia gravis unusually hazardous. In the critically ill patients with respiratory failure impending, one should defer radical treatment in the hope that intensive medical treatment will bring the patient through the crisis and permit operation at a later date. Those of mild degree should also be deferred in favor of medical therapy. The age is also a most important factor and the myasthenia patient should be considered as approximately twice the age in years. The authors report 8 operative cases with 2 considerably improved, 4 moderately and one slightly improved, and one postoperative death. The results in 121 other reported cases are 52 per cent classified as significantly improved. The incidence of thymic abnormalities in autopsies of patients dying of myasthenia gravis is about 50 per cent. The incidence of myasthenia gravis in patients with benign thymoma is almost 100 per cent. Myasthenia gravis is very rare in association with malignant thymoma.—*Thymectomy in the Treatment of Myasthenia*

Gravis, R. Adams & F. N. Allan, *Dis. of Chest*, September-October, 1947, 13: 486.—(E. A. Rouff)

**War Wounds of Chest.**—Patients with hemothorax should have an early thoracocentesis without air replacement. Large pulmonary metallic foreign bodies are best removed, smaller single ones are left *in situ*. Of 136 men with hemothorax, 46 developed empyema but 31 of the latter healed. Empyema is still a major complication of chest injury. The use of sulfa drugs and penicillin may often give a sense of false security.—*War Wounds of the Chest*, Lt. Comm. H. L. Jaffe & Comm. J. P. O'Connor, *Am. J. Roentgenol.*, August, 1947, 58: 183.—(J. E. Farber)

**Aneurysm of Pulmonary Artery.**—A true aneurysm of the pulmonary arterial trunk or of its major branches is very rare. The data are presented on 36 cases of pulmonary artery aneurysm, proved by autopsy and reported in the literature. Of 34 cases there were 18 men and 16 women. The average age of the male patients was 42.8 years, of the female patients 39.3 years. The main trunk of the pulmonary artery was involved in 89 per cent of the cases, only the right branch in 8 per cent, only the left branch in 3 per cent. The aneurysm was fusiform in 24 cases, saccular in 12 cases. The aneurysm was due to syphilis in 39 per cent, due to congenital anomalies in 47 per cent, due to subacute bacterial endarteritis, atheroma and trauma. The most frequent symptoms were: exertional dyspnea, cyanosis, edema, cough, hemoptysis and pain. The most characteristic signs were a harsh systolic murmur in the second or third intercostal space at the left border of the sternum, enlargement of the right heart and right axis deviation in the electrocardiogram. The roentgenological finding was a discrete, rounded shadow at the hilum, which on fluoroscopy showed pulsations. An additional case is reported. An attempt at surgical removal of the aneurysm was unsuccessful because of atheromatous calcifica-

tion of the artery wall. The patient died three days later. The autopsy findings were: saccular aneurysm of the right pulmonary artery, patent ductus arteriosus, atheroma of the right pulmonary artery, bilateral pulmonary arteriosclerosis.—*Aneurysm of the Pulmonary Artery: Review of the Literature and Report of a Case*, R. A. Deterling, Jr. & O. T. Clagett, *Am. Heart J.*, October, 1947, 34: 471.—(G. C. Leiner)

**Pulmonary Artery Pressure.**—The influence of breathing 10 per cent oxygen in nitrogen on pulmonary artery pressure and cardiac output was studied by the right heart catheterization technique in 4 normal men and in one man with aortic insufficiency. The diastolic pressure in the pulmonary artery rose from 6 mm. Hg to 13 mm. Hg on average, the systolic pressure from 21.9 to 35.1 mm. Hg, the mean pressure from 13.1 to 23 mm. Hg. The cardiac output decreased from 5.74 to 5.20 liters per minute on average. Pulmonary vascular resistance was almost doubled by breathing 10 per cent oxygen.—*The Influence of Short Periods of Induced Acute Anoxia upon Pulmonary Artery Pressures in Man*, H. L. Motley, A. Cournand, L. Werko, A. Himmelstein & D. Dresdale, *Am. J. Physiol.*, August, 1947, 150: 315.—(G. C. Leiner)

**Pulmonary Embolism.**—The cases of pulmonary embolism occurring in medical patients at the Massachusetts General Hospital in the five-year period from 1936 to 1940, during which conservative treatment was used, were compared with those occurring in the five-year period from 1941 to 1945, during which interruptions of the femoral veins were carried out. There were 122 cases in the first group and 151 cases in the second one. The incidence in male patients was higher. The great majority of the patients were over 40 years of age. The incidence of heart disease was 59 per cent in the first group and 70.8 per cent in the second one. The most frequent symptoms were pain in the chest, dyspnea and hemoptysis. A simultaneous rise of temperature, pulse rate and re-

spiratory rate were frequently the first indications of pulmonary embolism. The roentgenological diagnosis of pulmonary infarction was made in 33 per cent of the cases in the first five-year period and in 57 per cent in the second five-year period. The electrocardiographic findings were obscured by the coexisting cardiac disease in many cases. The pattern of the acute cor pulmonale was found in about one-fifth of the patients who were so examined. Since 1941 interruption of the femoral vein was carried out in 60 patients, since 1943 the operation was done bilaterally. The fatality rate for the operated patients was 28.3 per cent, for the nonoperated ones 50.7 per cent.—*Pulmonary Embolism in Medical Patients: A Comparison of Incidence, Diagnosis and Effect of Treatment in Two Hundred and Seventy-three Cases at the Massachusetts General Hospital in Two Five Year Periods (1936 to 1940 and 1941 to 1945 inclusive)*, J. Carloti, I. B. Hardy, R. Linton & P. D. White, J. A. M. A., August 23, 1947, 134: 1447.—(H. Abeles)

**Diaphragmatic Hernia.**—At the Mayo Clinic diaphragmatic hernias occur in a frequency of one to 2 per cent of all gastrointestinal (radiographic) examinations. Esophageal hiatal hernias comprise 98 per cent of all diaphragmatic hernias. There are four types of hiatal hernias: (1) congenitally short esophagus with thoracic stomach, (2) hiatal esophageal hernia with shortened esophagus, (3) esophageal hiatal hernia and (4) paraesophageal hernia through the hiatus. The most frequent symptom is substernal pain. Other symptoms are nausea, vomiting, bloating, belching heartburn, dysphagia and dyspnea. Bleeding often occurs. Hiatal hernias occur past age 40 in over 90 per cent of cases and twice as frequently in women as in men. Obesity and childbearing are causative factors. Radiographic diagnosis can be made if the esophagus is seen emptying into the stomach above the diaphragm and if the barium stream is retarded at the hiatus in the presence of a tortuosity of the lower part of the esophagus without dilatation.—*Roent-*

*genologic Characteristics of Diaphragmatic Hernia*, B. R. Kirklin & J. R. Hodgson, Am. J. Roentgenol., July, 1947, 58: 77.—(J. E. Farber)

**Histoplasmosis.**—*Histoplasma capsulatum* was the name given by Darling in 1905 in Panama to the causative organism of a disease with splenomegaly as one of its major features. He believed this organism to be a protozoan, but in 1913 da Rocha Lima concluded that the agent was a fungus. The subsequent cultivation of this fungus *in vitro* by De Mombreun and its experimental inoculation in monkeys is described. The disease is a "reticulo-endothelial cytomycosis," and is generally fatal in its systemic form. The organism will grow in the common sugar media as well as in blood agar and over a temperature range of 25° to 37°C. The disease is world-wide in distribution and its incidence probably much higher than is generally recognized. The disease occurs in the cat, the dog and probably in other animals. In the cat and dog the organism has been isolated from the peripheral blood; and the possibility of the flea and the tick being vectors is mentioned. The incidence of the disease in humans reaches a peak during the first year of life and again after 50. In a series of infants, postmortem examination showed lesions in the gastric and mesenteric lymph nodes, suggesting the digestive tract as portal of entry. *H. capsulatum* has been shown to be capable of traversing the intestinal mucosa without leaving a trace of its passage. Both sexes are equally susceptible to infection during the first ten years of life, but in adults the incidence is higher in the male. No racial or occupational predisposition occurs. The respiratory tract as a route of infection is discussed. The problem of pulmonary calcifications and the etiology of some of these is reviewed. There are points of similarity between histoplasmosis and tuberculosis as regards epidemiology, symptomatology and the nature of the pathological lesions produced. The lesions of both show necrosis and central caseation. Histoplasmosis must also be differentiated from Hodgkin's disease

(with which it may coexist), aleukemic leukemia and other blood dyscrasias, Banti's disease, atrophic cirrhosis, Addison's disease, cutaneous leishmaniasis and Kala-Azar. A few cases of subacute bacterial endocarditis have been reported in which streptococci could not be cultured, but in which at autopsy *H. capsulatum* was found in the valvular vegetations. The cutaneous and buccal lesions may suggest neoplasm. As regards treatment, the use of antimony has been disappointing. One case treated successfully with sulfanilamide and sulfathiazole by Balina, using large doses for a prolonged period, is referred to.—*Histoplasmosis*, P. Negroni, *Rev. Asoc. méd. argent.*, March 30, 1947, 61: 337.—(F. Perez Pina)

**Fungus Antigens.**—Three lots of histoplasmin, five of blastomycin, and heat-killed antigens prepared from yeast cultures of *Histoplasma capsulatum* and *Blastomyces dermatitidis* were tested on guinea pigs infected with these fungi. Evidently, the number of reactors among the various series of infected animals depended upon the particular lot and the dilution of antigen employed. Therefore, if various lots of those antigens were to be used for intracutaneous testing of sensitization to the respective fungi or their products, standardization of the various lots had to be employed; in these experiments a concentration of each lot was used which would detect a like percentage of sensitized animals. In this way fairly accurate comparisons of the potency of different lots of the antigens could be made. Markedly different dilutions of different lots might have to be employed in order to obtain a given percentage of reactors. It is important to determine the dosage or titer of a new antigen to be used. For practical and theoretical reasons the critical dosage or titer was "defined as the minimum amount of any antigen, which would detect sensitivity in approximately 80 to 90 per cent of a group of animals experimentally treated in such a way that all can be expected to become sensitive to an antigen prepared from the homologous organism." It was shown that a filtrate-type

antigen, such as histoplasmin or blastomycin, is as effective for intercutaneous testing as an antigen prepared from the parasitic phase of these two fungi, provided the titers are taken into consideration. In another series of animals only a small number of reactors were found although the same dilutions of the same lots of antigens were employed as in the first experiment; the value of the titer of each antigen varied markedly with the two groups. The explanation is that the animals of group 2 were tested at a time when their level of sensitivity was still low; the consideration of this level for the determination of the titer is very important. The animals of group 1 infected with histoplasma or blastomyces were also cross-tested with blastomycin or histoplasmin and their corresponding yeast-phase antigens, respectively. Most of the animals reacted to the heterologous antigens, but higher concentrations than with the homologous antigen had to be used to bring out the same percentage of reactors and the same size of the skin reaction. Infection with one fungus increases the sensitivity of an animal to a heterologous antigen, and when the dosage is increased the percentage of cross-reactions is increased by a much larger amount than that of the homologous reactions—which fact again stresses the need of determining the critical titer. The same guinea pigs were tested with Old Tuberculin, 0.1 cc. of a 5 per cent solution, and with coccidioidin in a 1:100 dilution. One animal infected with histoplasma and 3 infected with blastomyces gave small reactions to Old Tuberculin, but none of the infected animals reacted to coccidioidin.—*Studies of Fungus Antigens. 1. Quantitative Studies of Cross-Reactions between Histoplasmin and Blastomycin in Guinea Pigs*, A. Howell, *Pub. Health Rep.*, May, 1947, 62: 631.—(O. Pinner)

**Surface Phagocytosis.**—Chemotherapeutic agents, as ordinarily employed in acute bacterial pneumonia, are bacteriostatic. Final destruction of bacteria depends upon the defenses of the host. Recovery in pneumonia can occur long before any specific antibodies

are detectable. In the absence of antibodies, bacteria can be destroyed by phagocytes after being trapped against tissue surfaces such as the alveolar wall. When bacterial growth is inhibited and sufficient numbers of leucocytes are present, the bacteria may be destroyed after being trapped between the surfaces of the phagocytes themselves. In a purely fluid medium, where the bacteria cannot be trapped, no phagocytosis will occur. In the central portion of pneumonic lesions, where the exudate becomes more concentrated impeding bacterial movement, surface phagocytosis occurs most efficiently. Organisms which escape surface phagocytosis in the lungs and enter the lymphatics and blood-stream are most probably destroyed in the lymph nodes, spleen, liver and bone marrow. Although this has not been demonstrated, surface phagocytosis may occur in these organs as in the lungs. During systemic chemotherapy, phagocytic cells often fail to sterilize areas of abscess formation. This is due to the sluggish and non-viable leucocytes within the abscess and absence of normal tissue surfaces. The rôle of antibody in pneumonia is not minimized but this functions relatively late. Surface phagocytosis acts as an immediate defense reaction.—*The Mechanism of Recovery in Acute Bacterial Pneumonia*, W. B. Wood, Jr., *Ann. Int. Med.*, September, 1947, 27: 347.—(H. R. Nayer)

**Intravenous Oxygen Therapy.**—Extrapulmonary respiration was attempted as early as 1811. In 1916 and 1940 oxygen was given intravenously and reported to affect favorably hypoxic humans. Experiments on dogs between 1927 and 1943, however, produced pulmonary embolism and arterial hypoxemia, though animals in shock appeared to benefit. Inasmuch as the procedure seemed to be of potential value, an attempt has been made to

study it further. It was arranged to provide a steady flow of oxygen into the cubital vein; to obtain blood from the femoral artery; and to record the pulse, respirations, blood pressure, hematocrit and the heart action (by electrocardiogram). Six patients were studied in this way—4 of them were in a postoperative state, and were considered to have a stable cardio-respiratory condition; 2 were in a state of shock. (In general, they had hopeless neoplasms, or signs of hypoxemia.) During the administration of oxygen, 3 patients had signs of chest-pain, cough, tachypnea and restlessness—probably due to pulmonary embolism (similar to the “chokes” of nitrogen embolism at high altitudes). One patient had signs of cerebral hypoxia, one had the pain of myocardial hypoxia, and both patients having electrocardiograms were found to have the changes which occur in the “anoxic test” for angina pectoris. The amount of oxygen absorbed by venous blood was found to be insignificant. The bubbles of gas coalesce in the vein (as they do in a capillary tube filled with venous blood), and occlude the pulmonary arterioles, which are smaller in diameter than the bubbles. The resultant gaseous embolism causes a decreased pulmonary circulation, an arterial hypoxemia and a systemic hypoxia. These effects are probably intensified by reflex pulmonary spasm, and possibly by bronchospasm. Some of the ill-effects may be prevented by the preliminary use of atropine and papaverine. The diminished reflexes present in shock and anesthesia may allow the use of oxygen in those conditions. At present, however, the value of the procedure is doubtful and the occurrence of embolism makes it hazardous.—*Intravenous Oxygen and Pulmonary Embolism*, J. H. Sanders & I. M. Isoe, *Ann. Surg.*, August, 1947, 126: 208.—(W. H. Oatway, Jr.)





# VIRUS PNEUMONIA<sup>1</sup>

(Abstract)

MONROE D. EATON<sup>2</sup>

According to etiology, virus pneumonias may be classified into several disease entities, the most important being primary atypical pneumonia, influenza, psittacosis and Q fever. A summary of the clinical and epidemiological features of these diseases and their relation to milder respiratory illnesses without pneumonia will be presented. Serological tests for the laboratory diagnosis of virus pneumonia are useful in differentiating the various forms of the disease.

<sup>1</sup> Presented before the Medical Section, as part of a symposium on *Nontuberculous Pulmonary Disease*, at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 19, 1947.

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# PROPHYLACTIC IMMUNIZATION AND SPECIFIC THERAPY OF EXPERIMENTAL PNEUMONIC PLAGUE<sup>1,2</sup>

K. F. MEYER, S. F. QUAN AND A. LARSON

The past decade has witnessed noteworthy progress in the development of effective methods of immunizing against bubonic plague. The inherent deficiencies of active immunization have been recognized, but this has been counterbalanced by the discovery that sulfonamides in combination with antiplague serum or streptomycin impressively reduce the high case fatality rate. This progress does not apply to the problems of the destructive pneumonic plague, which in the past has been responsible for epidemics in Manchuria (1910-1911, 1919-1920) (1), and even in California (Oakland, 1919 and Los Angeles, 1924) (2). There is extensive proof that the secondary pneumonia of terminating fatal bubonic plague can cause primary plague pneumonia in contacts and set off an epidemic of primary pulmonary plague through man to man transmission independent of the rodent and insect vectors.

The bacteria isolated from bubonic and pneumonic plague are identical, and nobody has been able to confirm an early hypothesis (Polverini (3), Martini (4), Connal (5)) that the plague bacilli causing pneumonic plague have some special pulmonary tropism. In fact, experiments and epidemiological facts have demonstrated conclusively that whether one kind of plague or the other is produced by the invading agent depends entirely on the portal of entry. Theoretically, then, methods which have proved effective against infection transmitted through flea bites or the cutaneous portals of entry, should be protective or curative against the invasion of the plague bacillus *via* the respiratory tract. It is the purpose of this short communication to present the results of experiments undertaken to secure information basic to the adoption of prophylactic and therapeutic procedures against human pneumonic plague.

## EXPERIMENTAL PROCEDURE TO PRODUCE PNEUMONIC PLAGUE IN MICE, GUINEA PIGS AND COTTON RATS

In the past, many investigators experimentally produced primary plague pneumonia in guinea pigs, rats, rabbits, monkeys and tarabagans by forced inhalation of atomized bacilli, intratracheal injection or swabbing of the external nares with a cotton plug moistened in a plague culture. Mice were apparently not used.

The above methods of infection, aside from being potentially dangerous to the experimenters, frequently failed to produce infections. Since the evaluation of any method of immunization or the testing of drugs and antibiotics requires large

<sup>1</sup> Presented before the Medical Section, as part of a symposium on *Nontuberculous Pulmonary Diseases*, at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 19, 1947.

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series of animals, a relatively simple and safe procedure capable of producing pulmonary plague infection had to be developed. The methods of intranasal instillation so successfully and extensively used in virus research have proved equally efficient in producing pneumonic plague in mice, guinea pigs and cotton rats. To protect the experimenter from risk of exposure, the infections are executed in a specially constructed inoculation chamber (see figure 1). The animals are anesthetized with barbiturate, placed in the chamber on wire trays, and a suspension of highly virulent plague bacilli in buffered saline (4 to 8,000 organisms per 0.05 cc. per mouse and 0.3 cc. for guinea pigs) is carefully dropped with a graduated pipette into the nasal openings. As a rule, the deep inspiration of the properly anesthetized animals favors easy and complete aspiration of the drops. Until recovered from the anesthesia the mice remain in the special chamber, which is treated with an aerosol before the cages are removed to a special isolation room.

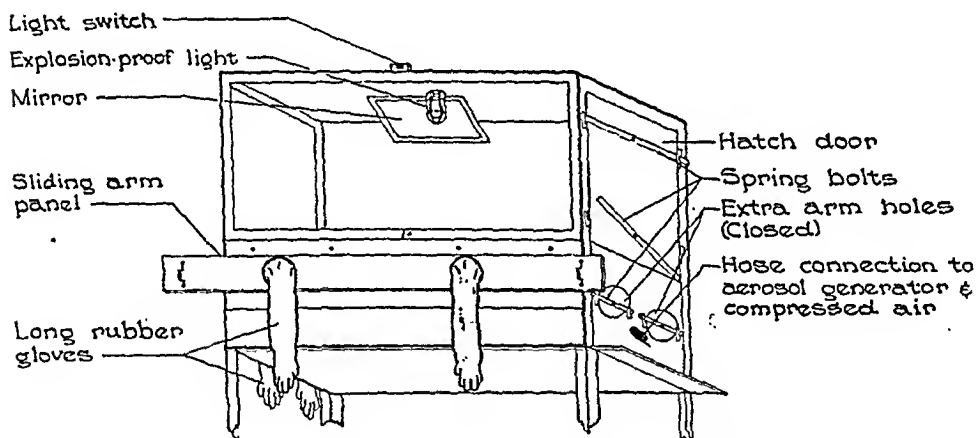


FIG. 1. Protective chamber for aerogenic infections

Quantitative cultural examinations of the lung tissues of animals sacrificed five to ten minutes after instillation of the suspension indicate (a) that the bacterial flora of the nasal passages is in part flushed into the bronchi, and (b) that on the average, one-tenth of the administered bacilli (200 to 700) has reached the deeper respiratory passages. Accurate determination of the number of plague bacilli is rendered difficult for the first twelve hours by the concomitant respiratory flora. However, by the twenty-fourth hour the rapidly increasing plague bacilli (up to 20,000 for the entire lung) predominate in the cultures. By the thirty-sixth hour, 2 to 4 million may be cultured from the entire mouse lung; by the forty-eighth hour, 20 to 500 million. At this stage, the blood stream is invaded and bacteremia is definitely demonstrable. The majority of mice and cotton rats succumb to the infection within seventy-two to ninety-six hours after the intranasal instillation of the plague bacilli. Guinea pigs, as a rule, are not visibly ill for the first two days but die suddenly between the third and fifth day.

The gross anatomical lesions in the mice vary slightly. In rapidly fatal infec-

tions a small amount of fluid is present in the chest cavities; all the lobes of the lungs are dark red, in a state of diffuse exudative hemorrhagic edema, or there is lobular red consolidation in the left or right anterior or diaphragmatic lobe. Edematous fluid oozes from the trachea and occasionally from the nostrils. Parenchymatous changes in the liver and kidneys as well as fatty hemorrhages in the adrenal complete the picture of a toxemia. When death is delayed by treatment or partial immunity for four to five days, the red consolidated lobes may float in a purulent stringy exudate in both pleural cavities; focal lobular grayish-red areas of consolidation covered with fresh fibrin are surrounded by deep red edematous lung tissue. The bronchial and mediastinal lymph nodes are then enlarged and edematous.

Since, in contrast to mice, guinea pigs are much more resistant to plague toxin, the gross lesions, aside from a generalized subcutaneous capillary injection, show little or no fluid in the pleural cavities. The lungs as a whole are voluminous, and portions of the apical or principal lobes are in different stages of red and gray hepatization. These primary areas of bronchial pneumonia are firm, contain no air, are irregular in outline and colored red, reddish-yellow and yellow. The pleural covering of these areas is rarely covered with fibrin. The bronchi and trachea are injected and covered with blood-streaked mucus. Bronchial and mediastinal lymph nodes are always enlarged, edematous and occasionally studded with early necroses; the regional lymph nodes of the neck and submaxillary space, as a rule, are not involved and the spleen is not enlarged. The infection is definitely confined to the respiratory tract.

That the process begins as a lobular bronchial pneumonia is amply proved by microscopic study of the progressive changes in the lungs of animals infected by the intranasal route. In these studies, mice and guinea pigs were sacrificed at intervals of six to twelve hours after the instillation of the culture, the lungs fixed in Bouin's solution and sections stained with Giemsa's solution according to the method of Wolbach. Briefly, the evolution of the lesions is as follows:

Between twelve to twenty-four hours after intranasal infection the grossly normal lungs reveal in the vicinity of some bronchioles focal cellular infiltration of the peribronchial lymphatic tissues. The bronchial epithelium is intact, but immediately below the muscle layer clusters of plague bacilli are embedded in masses of lymphocytes and polyblasts. This broncho-lymphatic phase is followed within twenty-four to thirty-six hours by exudation into the adjacent alveoli by serous and cellular elements. The exudate swarms with plague bacilli. The septa on the periphery of the alveolitis are engorged and the alveolar epithelium is swollen. Many of the alveoli contain desquamated cells, a few bacilli, leucocytes, serum and red cells. This second or pneumonic phase gradually spreads from a lobular process to cover ultimately the entire lobe. The right apical lobe or the anterior part of the left lobe may be particularly affected, with red exudation or an occasional abscess-like heavy cellular focal infiltration in which a small bronchus completely filled with leucocytes and bacilli shows various stages of necrosis. Plague bacilli are demonstrable in the capillaries and large blood vessels. At this stage—the septicemic phase—the *P. pestis* can be readily

cultured from the heart blood, bone marrow and spleen. The quick death of mice is, however, due to the mass of lung tissue invaded and the great amounts of toxin consequently absorbed. Thus, the evolution of the experimental plague infection of mice and guinea pigs infected intranasally, as established through histological examination of the lungs, corresponds in every respect with that of human pneumonic plague observed by Strong, Crowell and Teague (6) in the course of the epidemic in Manchuria in 1911.

The model of plague infection produced by intranasal infection is considered adequate for assessing the value of protective immunization, and the therapeutic efficacy of sulfonamides, antiplague sera and streptomycin.

#### EXPERIMENTAL PLAGUE PNEUMONIA IN VACCINATED ANIMALS

Several series of 20 to 50 mice previously injected subcutaneously with avirulent plague strains (A1122 and Tjiwidej) or formalin-killed antigens, which had been rendered particulate with alum, were infected intranasally or exposed to

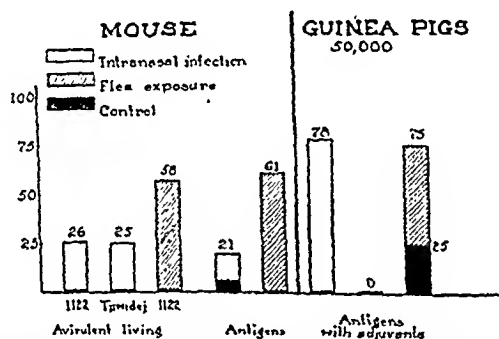


CHART I. Percentage of mice or guinea pigs immunized with avirulent living plague strains or alum precipitated antigens surviving intranasal infection or exposure to infected fleas.

plague-infected fleas in the so-called "mouse town." Similar experiments were conducted on guinea pigs, though only the immunizing effect of particulate alum-treated antigens has been so far tested on these animals. The data are summarized in chart I.

Both the avirulent plague strains and the antigen protected approximately 60 per cent of the mice against the customary massive infection induced by flea-bites; all the controls died. About 21 to 25 per cent of the animals resisted an intranasal infection. The experiments on guinea pigs were unfortunately marred by the seasonal resistance of this species, but it is demonstrated that their resistance against respiratory infection closely parallels their immunity against infective flea-bites. Nearly 80 per cent of the guinea pigs resisted the intranasal instillation of *P. pestis*. The differences in resistance between the mice and the guinea pigs is in part attributable to differences of susceptibility to plague toxin. Mice are susceptible, while guinea pigs are fairly resistant. Only intensive repeated immunization protects mice against toxins administered by the intra-

venous route. The resistance of a series of guinea pigs immunized with alcohol-killed plague bacilli with and without adjuvants was recently tested by three routes of infection. The data are summarized in table I and indicate that an antigen in suitable dosage with an adjuvant which protects against a subcutaneous or cutaneous flea-bite infection also immunizes against a moderately severe respiratory infection. These preliminary results show that the outlook for a prophylactic immunization against pneumonic plague is not as hopeless as previous reports would indicate.

TREATMENT OF EXPERIMENTAL PNEUMONIC PLAGUE WITH SPECIFIC  
CONCENTRATED RABBIT ANTIPLAGUE SERUM

At the request of the Surgeon General's Office two biological laboratories prepared, under the supervision of the Hooper Foundation, concentrated, highly potent antiplague sera in rabbits. These preparations cure 35 to 40 per cent of plague-infected mice when in a state of bacteremia. The outcome of experi-

TABLE I

*Guinea pigs immunized with alcohol-killed P. pestis antigen with and without  
adjuvants—1.5 mg. in two doses*

Percent surviving subcutaneous infection with 760,000 *P. pestis* (Shasta) or exposure to  
infected fleas or to intranasal infection with 34,500

ANTIGEN	SUBCUTANEOUS INFECTION	EXPOSED TO INFECTED FLEAS	INTRANASAL INFECTION
	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
Alcohol-killed.....	6/10—60	1/10—10	1/10—10
Alcohol-killed + alum.....	8/10—80	7/10—70	3/10—30
Alcohol-killed + Falba.....	8/10—80	9/10—90	7/10—70
Controls.....	0/10—0	0/10—0	0/12—0

ments with the preparations was interesting: the experimental results with mice resembled closely the experiences with antiplague therapy on man in India; when treatment was commenced at the stage of bacteremia the serum reduced the case fatality from 95 to 60 per cent, a curative effect of 35 per cent. When a number of persons in a household are exposed to pneumonic plague, passive immunization by the injection of antiplague serum has always been recommended. The results of serum therapy have with few exceptions been unfavorable, although most authorities agree that the antiserum prolongs the course of the pneumonic disease. Work with the mouse plague model lends some support to the clinical experiences. The data summarized in chart II indicate that antiplague sera administered within six hours after infection protect 90 per cent of the animals from progressive fatal disease. The course of the pneumonic process is definitely retarded when serum is administered on the twenty-fourth and thirty-sixth hour after intranasal infection, and approximately 35 per cent of the mice are cured. However, serum treatment, when delayed twenty-four hours longer (forty-eight hours), failed to save the mice from fatal pneumonic plague. The influence of the

serum on the infection is strikingly recognized at autopsy. Instead of the well known diffuse red exudative pneumonia involving the entire lobe, small yellowish abscess-like areas of necrosis protrude over the flabby edematous lung parenchyma. The serum tends to localize the infection to the early lobular alveolar pneumonic stages, but is apparently incapable of retarding multiplication of the plague bacilli, or preventing the damaging effect of the toxins. Anti plague serum of proved potency obviously has only a limited value in the treatment of pneumonic plague.

#### TREATMENT OF EXPERIMENTAL PNEUMONIC PLAGUE WITH SULFADIAZINE AND ANTIPLAGUE SERUM

Preliminary therapeutic experiments with sulfadiazine in experimental plague pneumonia of mice have shown it to have little or no effect when offered in the

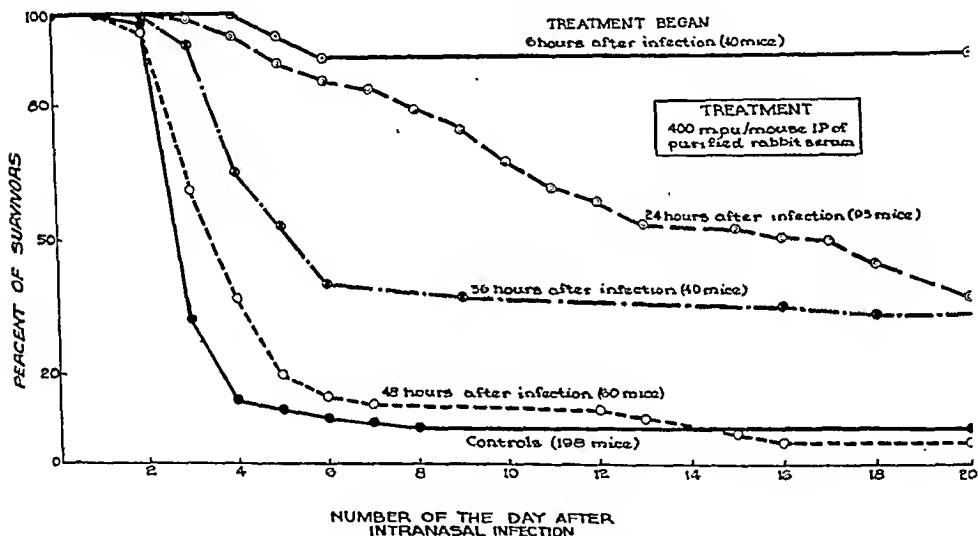


CHART II. Intranasal plague treated with anti-plague serum  
m. p. u. = mouse protection unit of serum.

drinking water in order to avoid continuous handling of the animals. Combination sero-chemotherapy, excellent in bubonic plague infections, proved superior to sulfa drug treatment alone. The data in chart III indicate that over 50 per cent of the intranasally infected mice may be cured when treatment is instituted early in the course of the disease. The optimum dosage of drug and serum has not been determined. It has been found that continuous handling and passing of the stomach tube on mice with pneumonic plague not only endangers the operator but introduces many uncontrollable factors which adversely affect the therapeutic efficacy of the drug and serum.

#### TREATMENT OF EXPERIMENTAL PNEUMONIC PLAGUE WITH STREPTOMYCIN

Intensive experimentation during the past three years has shown that streptomycin in the concentration of 1.9 micrograms per cc. inhibits 20,000 *P. pestis* in



2 cc. hormone broth for six days. The addition of 0.063 mg./cc. of the antibiotic to hormone broth culture of a virulent *P. pestis* (approximately 100,000 organisms per cc.) proved bactericidal in twelve hours and 0.25 mg./cc. in ninety minutes, while 0.5 mg./cc. sterilized in fifteen minutes or less. Streptomycin is thus far superior to sulfonamides; it will cure 100 per cent of the advanced bubonic plague infections in mice treated with 0.05 to 0.80 mg. every three hours, or a daily streptomycin dose of 0.40 to 0.65 mg. for three to six days. The rate of survival of infected animals is directly proportional to the amount of streptomycin administered in their treatment. These observations, amply confirmed in guinea pigs and recently on human bubonic plague infections in Argentina, provoked investigations on experimental pneumonic plague infections in mice. The data in chart IV prove that pneumonic infection exhibiting in the thirty-sixth hour definite lobular lesions containing several million plague bacilli,

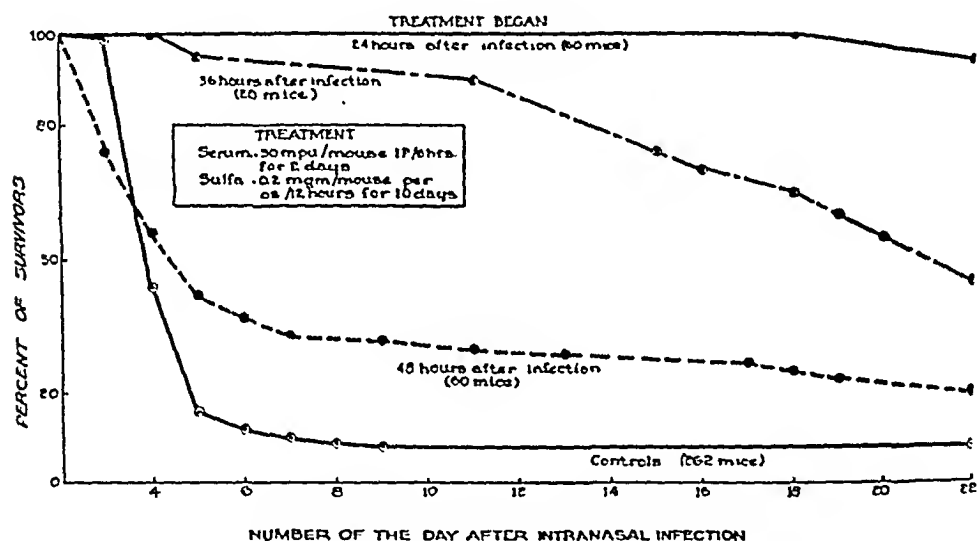


CHART III. Intranasal plague treated with serum and sulfadiazine

may be cured in 90 to 95 per cent of the mice with 200 to 400 micrograms streptomycin administered at six hour intervals for ten days. As might be expected, smaller doses or treatment of more advanced infections markedly reduces the chances for an effective cure.

The technique of bacteriological autopsies introduced by Jawetz and Meyer (7) in the study of experimental plague was used in this study on the curative effect of streptomycin. The results of one experiment are presented in chart V.

Following the intranasal instillation of 2,500 highly virulent plague bacilli (strain Shasta) into a large series of mice, groups of 4 animals were sacrificed at regular intervals. The lungs and spleens were removed aseptically, the tissues triturated with sand, extracted with sterile broth, and proper dilutions plated on blood agar. The progressive increase from 200 to 700 organisms per lung immediately after infection to an average of 2,000,000 bacilli on the thirty-sixth hour was remarkably uniform. At the thirty-sixth hour, when treatment with 200

micrograms of streptomycin was instituted, a septicemic stage was already present and plague bacilli were cultured from the spleen. Six hours after treatment had begun, the number of plague bacilli had been reduced to approximately 60,000, while in the untreated it had advanced to 10,000,000. Between the twelfth to

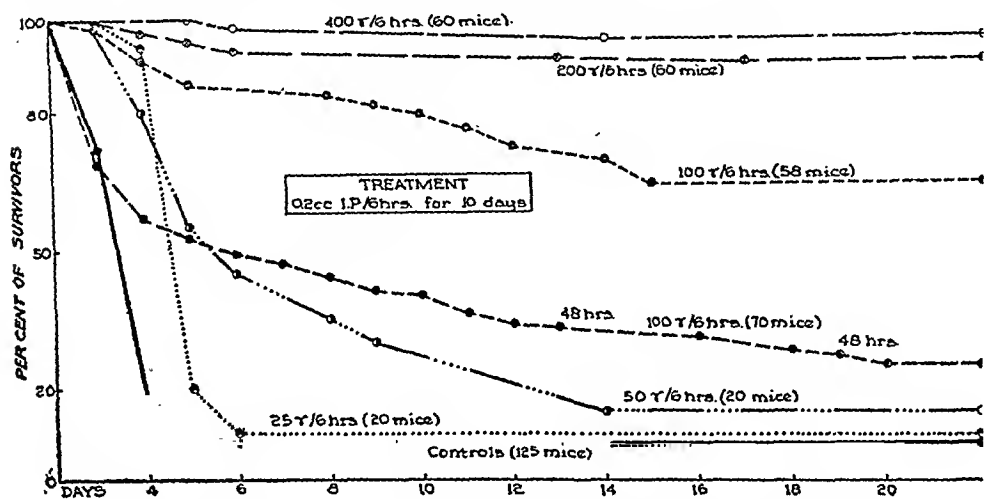


CHART IV. Streptomycin in the therapy of the 36-hour intranasal plague

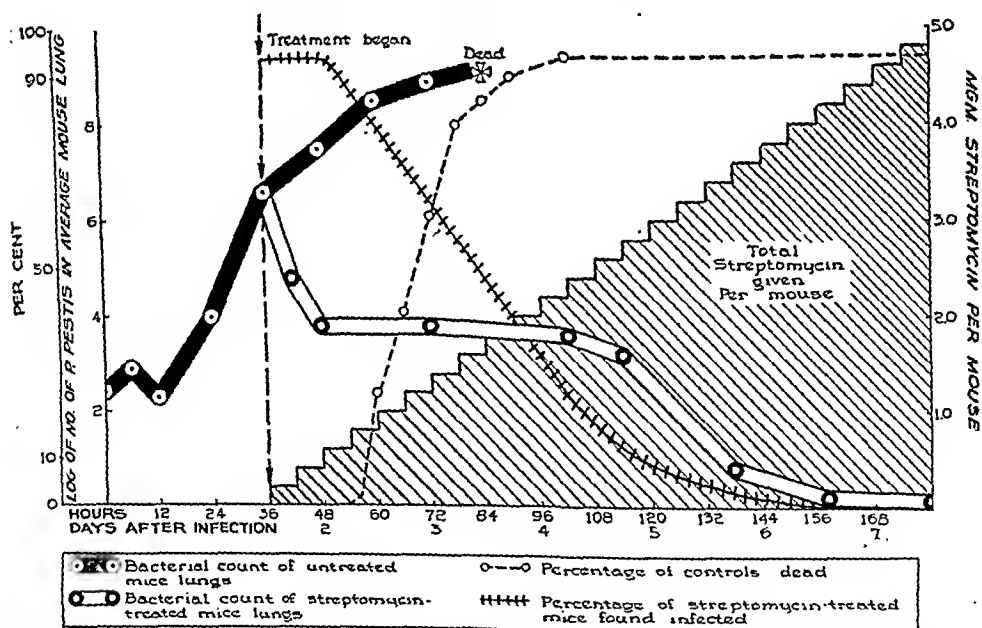


CHART V. Bacteriological study of intranasally-infected streptomycin-treated mice. Progressive sterilization of pneumonic plague lesions in mice treated with streptomycin.

twenty-fourth hours of treatment the spleens invariably became sterile and the counts for some of the lungs were below 500 organisms. By the ninety-sixth hour after infection, when all of the untreated mice had died, the lungs and bronchial lymph nodes of the treated mice were either sterile or contained a few

thousand plague bacilli in the abscess-like patches of pneumonia. The grayish glassy foci resembling those in mouse pneumonitis were invariably sterile. As late as the twenty-fifth day after infection and twelve days after termination of treatment, residuals of the existing plague pneumonia could be seen at autopsy of the sacrificed mice: circumscribed reddish areas in the lungs or complete carnification of the entire left or right apical or intermediate lobes. Enlarged bronchial and mediastinal lymph nodes and spleens gave evidence of intense activity in the cellular immunity mechanism. Plague bacilli have yet to be isolated from the lung tissues or lymph nodes one hundred hours after treatment with streptomycin has begun.

These results fully attest to the remarkable therapeutic efficacy of a total of 5 mg. of streptomycin in experimental pneumonic plague of mice. They justify an expectation that the antibiotic will be equally effective in human pneumonic plague if administered early and in adequate dosage. Since mice are far more susceptible to plague than man, it is anticipated that a total of 20 to 40 g. of streptomycin in daily dosage of 4 to 6 g. for at least six to ten days will reduce the frightful human case fatality rate from this form of plague infection to 10 per cent or even lower.

#### CONCLUSIONS

(1) Intranasal instillation of 2,000 to 25,000 highly virulent plague bacilli produces in mice, guinea pigs and cotton rats a primary pneumonia which is anatomically indistinguishable from that observed in man.

(2) Active immunization with avirulent strains of *P. pestis* or chemically killed plague bacilli in the form of particulate antigens confers on mice a definite and on guinea pigs a marked protection against an intranasal challenge infection.

(3) Concentrated antiplague rabbit sera possess prophylactic and, to a slight degree, curative values in pneumonic plague.

(4) Sulfonamides are not very effective in experimental pneumonic plague. However, when combined with antiplague serum, their therapeutic value, definite in bubonic plague, is equally demonstrable in the pneumonic type.

(5) Streptomycin is thus far the most effective therapeutic agent known for the treatment of plague infections, both bubonic and pneumonic. Over 90 per cent of experimentally infected mice, when in the septicemic state of lobular plague pneumonia, may be cured with 5 mg. of streptomycin. It is recommended that human pneumonic plague be treated early in the course of infection with daily doses of 4 to 6 g. of streptomycin, and that treatment should continue for not less than six to ten days.

#### CONCLUSIONES

##### *Inmunización Profiláctica y Terapéutica Específica en la Peste Neumónica Experimental*

1. La instilación intranasal de 2,000 a 25,000 bacilos pestosos virulentísimos produce en los ratones, cobayos y ratas algodonerías una neumonía primaria que, anatómicamente, es indiferenciable de la observada en el hombre.

2. La inmunización activa con cepas avirulentas de *P. pestis* o con bacilos pestosos matados químicamente, en forma de antígenos particulados, otorga protección, a los ratones bien definida y a los cobayos pronunciada, contra una infección intranasal provocativa.

3. Los sueros antipestosos concentrados de conejo poseen propiedades profilácticas y levemente curativas en la peste neumónica.

4. Las sulfonamidas no son muy eficaces en la peste neumónica experimental; pero, combinados con el suero antipestoso, su valor terapéutico, bien definido en la peste bubónica, es igualmente observable en la forma neumónica.

5. La estreptomycina constituye hasta la fecha la terapéutica más eficaz conocida en las infecciones pestosas, tanto bubónicas como neumónicas. En el período septicémico de la neumonía lobulillar pestosa puede curarse con 5 mg. de estreptomycina a más de 90 por ciento de los ratones infectados experimentalmente. Recomiéndase que la peste neumónica humana sea tratada bien temprano en su evolución con dosis diarias de 4 a 6 gm. de estreptomycina, continuando el tratamiento por lo menos de seis a diez días.

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# ACTINOMYCES IN CHRONIC BRONCHOPULMONARY INFECTIONS<sup>1</sup>

EARLE B. KAY<sup>2</sup>

The presence of actinomyces in the mouths and throats of healthy individuals was demonstrated first by Lord (1) in 1911. The frequency with which actinomyces can be isolated from and about carious teeth and tonsillar crypts has since led observers to consider the organism as part of the normal bacterial flora. Bronchopulmonary actinomycosis has been considered to be a rare and often fatal disease. It has not been appreciated that actinomyces can commonly be demonstrated in chronic bronchopulmonary infections. Yet when one realizes the part played by the aspiration of oral and pharyngeal exudates in the production of aspiration atelectasis, pneumonia, lung abscesses and chronic pulmonary suppuration, one might expect to find this organism in such infections in the same frequency as other mouth organisms.

The ciliary and cleansing peristaltic action of the normal bronchi in healthy persons prevents minor degrees of aspirated flora from assuming clinical significance. If bronchial or bronchiolar occlusion with its concomitant atelectasis results from this aspirated material and remains unrelieved, an aspiration pneumonia results. Under these anaerobic conditions the saprophytic micro-aerophilic actinomyces may assume pathogenic propensities. Approximately ten per cent of the cases of actinomycosis is caused by the aerobic species, *Nocardia*. The remaining 90 per cent is caused by the micro-aerophilic species, *Actinomyces Israeli*, with which this paper is concerned.

The frequency with which a diagnosis of pulmonary actinomycosis is made depends upon the frequency with which one requests a bacteriological examination for actinomyces, the amount of exudate provided, the experience of the bacteriologist and the care exercised in culturing methods. The frequency with which actinomyces may be found in chronic bronchopulmonary infections was stressed in a previous paper (1). During one period of six months at the Chest Center at Kennedy General Hospital during the war, 240 patients with chronic bronchopulmonary infections were carefully studied for the presence of actinomyces. Actinomyces were isolated from the sputum in 109 of these patients. They were also isolated from exudate obtained bronchoscopically in 65 of these 109 patients. The exudate aspirated from lung abscesses in 6 patients, and from the sinus tracts of 2 patients also contained actinomyces in combination with other organisms. Thirty-seven of the 65 patients having actinomyces in bronchial exudate had bronchiectasis with varying degrees of pneumonitis. The actinomyces in patients with bronchiectasis were felt to be saprophytic and not clinically important under aerobic conditions. In another 8 patients the only apparent disease was a moderately severe chronic bronchitis. There was roent-

<sup>1</sup> Presented before the Medical Section, as part of a symposium on *Nontuberculous Pulmonary Diseases*, at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 19, 1947

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gen and clinical evidence of either aspiration pneumonia, lung abscess or extensive pulmonary suppuration in 20 patients. Actinomyces were isolated and cultured from these patients from exudate obtained bronchoscopically or aspirated from lung abscesses, and in 6 instances taken directly from the lung following pulmonary resection. Recently I saw a patient with a postpartum chronic lung abscess requiring resection of the right upper lobe in which actinomyces, trichomonads, spirochetes, fusiform bacilli, as well as the more common pyogenic organisms were found. Another recent patient developed bilateral lung abscesses secondary to an aspiration pneumonitis following a partial gastric resection. Actinomyces were found in the material aspirated from the abscesses.

In approximately 50 per cent of all patients with bronchiectasis, chronic lung abscesses and extensive pulmonary suppuration, actinomyces were isolated when carefully looked for. Prior to this study similar cases were being treated in large numbers but no actinomyces were found, mainly because such examinations and cultures were only occasionally requested, and the bacteriologist was not as familiar with fungus identification.

The finding of actinomyces with such frequency caused considerable concern because previous experience had related only to isolated cases. Care was exercised to verify the identity of this supposedly pathogenic non-acid fast anaerobic ray fungus. Sulfur granules could be seen on direct examination in only one fourth of the specimens. Microscopic identification of the mycelia from the smear was possible in 13 of the 20 patients having chronic pulmonary infections apart from those having bronchiectasis. In all instances the actinomyces grew on culture. Actinomyces were also cultured from the gastric washings of 2 patients. Actinomyces were usually verified on at least four to five examinations.

Sputum is an unreliable source for examinations for fungus infections because of the contamination by the bacterial flora of the mouth. If sputum is used for examination for fungi it should be fresh and obtained only after the patient has cleansed his teeth and irrigated his mouth. The use of an oxidizing or adstringent mouth wash prior to collecting the specimen is essential. The use of bronchoscopic exudate, or that obtained directly from the lung at the time of either drainage or resection is a more reliable source.

Actinomycosis differs from many other more specific infections, for actinomyces are rarely found to the exclusion of other organisms which may also play a part in the production of the disease process. Mixed infection is the rule in chronic pulmonary infections secondary to aspiration. Not uncommonly the actinomyces, which are slow to grow in culture, may be overgrown by other bacteria and not recognized. In most of the reported descriptions of patients with pulmonary and thoracic actinomycosis, the presence of other organisms or a mixed infection is usually only briefly mentioned, the main emphasis being directed to the actinomyces. Some observers (3, 4, 5) have stressed the importance of mixed infections in actinomycosis, believing that the other organisms were of significance in either initiating the infection or producing a more rapid spread of the infection and a greater inflammatory reaction by the tissues. Among the more common organisms usually found are staphylococci, streptococci, spirochetes and fusiform bacilli.

The following procedure was followed in the identification of the actinomyces. Exudates obtained bronchoscopically and material aspirated from lung abscesses at the time of operation were taken directly to the bacteriology laboratory. A small amount was placed in a Petri dish containing saline and examined against a black background. If typical sulfur granules were present, or small flecks of gray or white material were seen, they were removed with a loop, placed on a slide and crushed with a cover slip. Microscopical identification depended upon masses of filaments showing some branching and radiation toward the periphery. Beading or clubbing was not always seen. Acid-fast and Gram stains were then used to determine the staining characteristics. These organisms are Gram positive and not acid-fast. Granules from the sterile Petri dish were then inoculated into one tube of Brewer's thioglycolate, two tubes of enriched agar, two tubes of Sabouraud's dextrose agar slants and one tube of veal or beef infusion agar. They were incubated at 37°C. for three weeks. In the shake-tubes the fungus grew about one centimeter below the surface, and it appeared fuzzy white.

It is debatable as to whether the cases reported here should be classified as pulmonary actinomycosis or as aspiration pneumonia, lung abscesses or pulmonary suppuration in which this fungus is present. It might be assumed that the terms "pulmonary actinomycosis" should be applied only to those patients who have pulmonary suppuration associated with chest wall sinuses from which this organism can be isolated. However, it is known that pyogenic as well as tuberculous infections may also have draining sinuses secondary to underlying pleural and pulmonary involvement. The term "pulmonary actinomycosis" is then comparable to the terms "streptococcal", "staphylococcal" and "spirochetal" pneumonitis. There is no question that actinomyces under certain conditions may predispose to chronicity and as such may be partially responsible for the development of chronicity in broncho-pulmonary infections.

With accumulated experience, it became apparent that actinomyces in bronchial and pulmonary exudates were rather common and not as clinically significant as originally thought. As is well known, pulmonary suppuration is a very chronic condition in itself. The prognosis of such infections is greatly influenced by the mechanical factors of bronchial occlusion or drainage, tissue destruction, fibrosis and avascularity.

If the assumption is true that actinomyces may be commonly found in aspiration pneumonias and lung abscesses and that the infection remains local in the lung for some time before causing pleural and chest wall involvement, it is mandatory for the clinician to establish the diagnosis early and to give the appropriate treatment.

Pathologically, the initial lesion was usually lobular in distribution and pneumonic in type. A pneumonia secondary to atelectasis was thought to develop which progressed in a number of instances to suppuration and abscess formation. The abscesses were burrowing in character. There was a marked fibrous reaction. Many of the alveoli were replaced by scar tissue. The granulation tissue about the abscesses was highly vascular. It was in this granulation tissue or within the purulent exudate that the actinomyces were most commonly found.

As the infection spread the interlobar fissures became obliterated and the adjacent lobes were involved. Pleural involvement may occur early, causing the lung to become densely adherent to the chest wall. If the infection remains uncontrolled empyema and chest wall sinuses may result. The diagnosis must remain mainly a bacteriological one, for the pathological process may be indistinguishable from that seen in nonspecific chronic inflammatory conditions unless a section should contain an actinomycotic granule. Only one such granule was found in the sections examined in spite of the repeated presence of actinomyces grown in cultures. The presence of the actinomycotic granule is felt to depend on the resistance of the host.

The 8 patients with chronic bronchitis in whom actinomyces were isolated had had a harsh productive cough in most instances for many months and occasionally for several years. The sputum was frequently blood tinged. They were all suspected of having bronchiectasis. Bronchoscopic examination revealed the mucous membrane of the entire tracheobronchial tree to be extremely hyperemic and granular. The bronchograms were normal. These patients obtained marked relief by the intratracheal instillation or inhalation of penicillin, and in 3 patients actinomyces as well as streptococci disappeared from the bacterial flora of the tracheobronchial tree with this treatment. Repeated bronchoscopic examination three weeks following the treatment showed considerable improvement of the hyperemia.

The clinical picture of the 37 patients with bronchiectasis in whom actinomyces were isolated from the sputum and exudate obtained bronchoscopically did not differ appreciably from those patients with bronchiectasis in whom actinomyces were not found. It was felt, however, that the sputum in some instances was more copious in amount, foul in odor, and more frequently bloody. Lobectomies were performed for these patients as treatment for the bronchiectasis and not because of the presence of actinomyces. At first additional precautions were taken when actinomyces were present. Considerable discussion arose as to the advisability of performing operative procedures in the presence of actinomyces for fear of spreading the infection and the development of sinuses. Increased dosages of sulfonamides and penicillin were given pre- and postoperatively but this was later found to be unnecessary. In no instance was the postoperative course complicated by actinomycotic empyema or draining sinus. These patients were not considered to have actinomycosis even though actinomyces were isolated which were indistinguishable from those isolated from patients with chronic lung abscesses and draining chest sinuses.

The clinical course and response to treatment of patients with chronic pneumonitis, lung abscesses and pulmonary suppuration appeared to depend on the chronicity and severity of the infections. The disease process for the most part was seen in patients with poor oral hygiene. The onset of the disease as noted in soldiers usually followed episodes of exposure, fatigue and weight loss associated with combat or military life. In 3 the pulmonary complaints followed upper respiratory infections and in 2 the extraction of teeth. One of the 2 most recent cases treated was a woman who developed aspiration pneumonia following



delivery. The other was a man with bilateral aspiration pneumonia following a gastric resection. In several it was felt that an episode of drunkenness initiated the illness.

The onset of the disease was characterized by chills, fever and productive cough. Later, pain in the chest and increasing debility developed. Bloody sputum was present in all patients at one time or another and in 3 cases pulmonary hemorrhage was a prominent feature. Most of the patients had been treated with varying dosages of penicillin and sulfonamides with temporary symptomatic improvement, only to be followed by exacerbations in most instances after the chemotherapy or antibiotic had been discontinued.

There is nothing characteristic about the history or physical findings in patients with early pulmonary actinomycosis that is sufficiently specific to be diagnostic. It simulates the other chronic pulmonary infections. It is a progressive debilitating disease characterized by a foul productive cough. The presenting signs and symptoms depend upon the stage in which the patient is first seen. There may only be the evidence of the pneumonic lesion if seen early, or if seen late, evidence of empyema and chest wall sinuses may be present. The pulmonary involvement was unilateral in 16 and bilateral in 6 patients. The roentgen findings may also be varied, ranging from pneumonitis to empyema and multiple rib destruction. The mid-lung field was involved in 11 instances, the upper in 8 and the lower in 3. It may be indistinguishable from tuberculosis or chronic pulmonary suppuration. The bronchoscopic appearance of the tracheobronchial tree was that of a nonspecific chronic inflammation. The mucous membrane was usually intensely hyperemic and granular. No evidence of ulceration was noted. In all chronic pulmonary disease of undetermined etiology, the clinician should suspect the possibility of a fungus infection and request appropriate examinations. When the diagnosis of fungus infection and particularly actinomycosis is once established the clinical course and response to therapy depend largely on the state of chronicity and severity of the infection.

The results of treatment employing such time-honored measures as potassium iodide, thymol, vaccines and roentgen therapy have in general proved unsatisfactory. Greater success was reported following sulfonamides and penicillin. It must be emphasized at this time that these chemotherapeutic drugs and antibiotics frequently fail to obtain a cure and should not be continued unduly long when only symptomatic improvement and not actual improvement as noted roentgenologically is obtained. By so doing, extension of the localized disease to the pleura and chest wall may occur, thereby preventing or complicating surgical extirpation of the diseased tissue.

Wangensteen was one of the first to emphasize the importance of surgical drainage in the treatment of actinomycosis; and most successfully treated patients have had some form of surgical therapy. Of the 18 cured patients with actinomycosis reviewed by him from the literature between 1892 and 1932, and also one of his own patients, all but one were treated surgically by drainage or rib resection.

The patients in this series were again treated with large doses of penicillin, a

combination of penicillin and sulfadiazine, or sulfadiazine alone in an attempt to determine the efficacy of these medications. Though the infection appeared to respond to each of these three methods, penicillin, or penicillin in combination with sulfadiazine appeared to be most effective. It is essential that penicillin and sulfadiazine be given in large dosages and continued for a long time after roentgen and clinical improvement, to prevent recurrence. The dosage employed was 50,000 units of penicillin every three hours intramuscularly for a period of eight to twelve weeks, and in some instances for a longer period. A blood level of 10 mg. per cent of sulfadiazine was maintained.

Those patients with less severe infection (7) with roentgen evidence of pneumonitis without evidence of cavitation who appeared to have good bronchial drainage responded fairly well to penicillin and sulfadiazine therapy. These patients had had their disease from two to five months. Three patients healed with large doses of penicillin either alone or in combination with sulfadiazine. A fourth has considerable residual pleural thickening but no evidence of active infection. The fifth patient healed almost completely following a two-month course of therapy, but the infection recurred after the penicillin was discontinued. There was no response to a second course of penicillin and sulfadiazine, and the infection then spread to the opposite lung. In the sixth patient, whose pneumonitis was secondary to postoperative atelectasis, spread of the infection and bilateral cavitation developed during an intensive course of penicillin and sulfadiazine. Surgical drainage of three abscesses was necessary before healing resulted. The seventh patient required pulmonary resection because of incomplete clearing and recurrence of symptoms.

When cavitation was present, less benefit from chemotherapeutic and antibiotic therapy resulted. The general symptoms of toxemia were allayed and there was some symptomatic improvement. This was frequently associated with roentgen clearing of the pneumonitis surrounding the cavitation. In only one patient did the abscess heal on conservative measures alone. Three patients healed following surgical drainage in conjunction with penicillin or sulfadiazine. One patient following drainage continued to have residual pneumonitis and a draining sinus. No follow-up observation on this patient has been obtained. Two other patients noted partial improvement following drainage but pneumonitis and cavitation persisted and resection of the diseased tissue by lobectomy was required. In no instance was the postoperative course complicated by actinomycotic involvement.

In more extensive cases of pulmonary suppuration failure to respond to conservative measures was noted. Pneumonectomy was necessary in 2 patients before healing occurred and resection of the diseased tissue by lobectomy was performed in 3 other instances. Two of the latter cases had previously had drainage of lung abscesses with only partial benefit. Four of the 7 patients having pulmonary resections were treated postoperatively with sulfadiazine in combination with penicillin and the other 2 with penicillin alone. Two patients have now been well for over two years, the others except one for over a year.

The pulmonary tissue found to be involved at the time of operation was con-

siderably more extensive than the roentgen findings had indicated preoperatively. The lung tissue was hard, consolidated and fibrotic. Because of its consistency and firm attachment to the chest wall it was occasionally difficult to differentiate from malignancy. Extensive pleural adhesions and symphysis were present in 6 of the 7 operated patients. The pulmonary fissures were obliterated by adhesions and inflammatory tissue necessitating in several instances transection between clamps. Examination of the surgical specimen again showed marked fibrosis about multiple necrotic and burrowing abscesses, the walls of which were covered by dirty, greyish-appearing granulation tissue. The actinomyces were readily isolated from these abscesses in each case. Because of the extensive destruction of lung tissue noted microscopically, it is now felt that patients recover faster and have less likelihood of recurrence in case cavitation is present if the diseased tissue is removed by pulmonary resection rather than treated by drainage. The abscesses in many instances are multiple and small and impossible to drain completely.

One patient with draining chest sinuses secondary to pulmonary and pleural involvement healed after a four-week course of sulfadiazine. He remained healed for approximately five months with only evidence of residual pleural thickening when lumbar and perinephric abscesses developed. These have required drainage on several occasions but still tend to recur. The lungs have remained clear. A second patient with multiple rib involvement bilaterally continued to drain intermittently even after four rib resections.

#### SUMMARY

Bronchopulmonary actinomycosis has been considered to be a rare and often fatal disease. It has not been appreciated that actinomyces can commonly be demonstrated in chronic bronchopulmonary infections. The frequency with which a diagnosis of pulmonary actinomycosis is made depends upon the frequency with which one requests a bacteriological examination for actinomyces, the amount of exudate provided, the experience of the bacteriologist with fungus identification, and the care exercised in culturing methods. Examination of 240 patients with chronic bronchopulmonary infections showed actinomyces to be present in the sputum of 109 of these patients, and in the exudates obtained bronchoscopically in 65. Actinomyces were always found in a mixed infection and probably were significant clinically in the development of chronicity only under anaerobic conditions. The response to conservative and surgical therapy is discussed. The prognosis depends largely upon the severity of the infection and the degree of destruction present when first seen. Favorable response to therapy occurred with the use of chemotherapeutic drugs and antibiotics, particularly when these were used in conjunction with surgical therapy. In 9 patients healing resulted only after resection of the diseased pulmonary tissue by lobectomy or pneumonectomy. Surgical therapy for bronchiectasis, lung abscess or pulmonary suppuration was not complicated postoperatively by the presence of actinomyces.

## SUMARIO

*El Actinomiceto en las Infecciones Broncopulmonares Crónicas*

La actinomicosis broncopulmonar pasa por ser una enfermedad rara y a menudo letal, sin tomarse en cuenta que puede encontrarse corrientemente el actinomiceto en las infecciones broncopulmonares crónicas. La frecuencia con que se hace el diagnóstico de actinomicosis pulmonar depende de la frecuencia con que se solicite un examen bacteriológico para actinomicetos, la cantidad de exudado facilitada, la experiencia del bacteriólogo en la identificación de hongos y el cuidado desplegado en las técnicas de cultivo. El examen de 240 enfermos con bronconeumopatías crónicas reveló actinomicetos en el esputo de 109 de ellos y en el exudado obtenido broncoscópicamente en 65. Encontráronse siempre actinomicetos en las infecciones mixtas y probablemente sólo en condiciones anaerobias revestían importancia clínica en la producción de cronicidad. Discútese la respuesta a la terapéutica conservadora y la quirúrgica. El pronóstico depende en gran parte de la gravedad de la infección y de la destrucción presente al observar el caso por primera vez. Obtúvose respuesta favorable al tratamiento al emplear drogas quimioterapéuticas y antibióticos, sobre todo si se combinaban con la cirugía. En 9 enfermos sólo se logró la curación después de resecar el tejido pulmonar afectado con una lobectomía o neumonectomía. La presencia de actinomicetos no complicó postoperatoriamente la intervención cruenta por bronquiectasia, absceso pulmonar o supuración pulmonar.

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## THE USE OF COCCIDIOIDIN<sup>1,2</sup>

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Coccidioidin, the filtrate of liquid cultures of *Coccidioides immitis* used as a skin testing material, has become very important in the diagnosis of coccidioidal infection. It is our purpose to present clinical and experimental data supporting its use and indicating certain limitations which impair its usefulness unless they are appreciated.

A variety of coccidioidins has been prepared. The first successful coccidioidin, that of Davis (1), was a suspension of the fungus rather than a filtrate. Previously, Cooke (2) had reported only equivocal results with several materials including mycelial and sporangial ("spherule") "emulsions" and a heat concentrated glucose broth filtrate. Cummins and Saunders (3) also had used several preparations of broth filtrates heat killed and concentrated to one-tenth volume over a water bath. They concluded from animal experiments that the reactions were nonspecific, although they reported a definite reaction in a patient with coccidioidal granuloma. Hirsch and Benson (4) and Hirsch and D'Andrea (5) prepared coccidioidin as filtrates from cultures of placenta extract broth and also ammonium lactate synthetic medium. They showed that these filtrates contained a substance producing skin reactions in infected patients and animals comparable to those evoked by tuberculin. This active principle, produced by various strains of *Coccidioides*, withstood heating, was mostly precipitated by two parts of alcohol and appeared to be a polysaccharide which contained 3 to 4 per cent nitrogen. They also believed it sensitized animals. Subsequent coccidioidins have varied between meat infusions and synthetic media. Jacobson was the first to use coccidioidin in any considerable number of human cases (all coccidioidal granuloma or progressive disease). The coccidioidin used by him was a fil-

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<sup>2</sup> These investigations are an activity of the Commission on Acute Respiratory Diseases, Army Epidemiological Board, Office of the Surgeon General, U. S. Army, Washington, D. C. They have been carried out by the Department of Public Health and Preventive Medicine, Stanford University School of Medicine. From 1937 to 1941 these studies were supported by the Rosenberg Foundation.

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trate first of Sabouraud's bouillon (6a) and then of glucose broth (6b). He also refers (6b) to "exotoxin" and "endotoxin," although no one has ever demonstrated any true "toxin" harmful to normal animals, Jacobson (6a) himself having indicated its innocuousness. The coccidioidin of Beck, Traum and Harrington (7) which elicited positive intracutaneous reactions in infected cattle was autoclaved beef broth filtrate of *Coccidioides* cultures concentrated to half volume over a water bath. Previously Giltner (8) had used a similarly concentrated beef broth filtrate and a mycelial broth suspension for subcutaneous testing of infected animals without eliciting a response. The coccidioidin used by Hurwitz, Young and Eddie (9) in the first skin-testing survey to be reported was an old whole broth culture, heat killed, dried and suspended in phenolized saline as the equivalent of a 1:10 dilution. Kessel (10a) prepared a coccidioidin widely used in Southern California and also by Gifford (11) in her pioneer studies of Valley Fever (coccidioidal erythema nodosum). This was a veal broth culture, heat killed, in which the multiple strain *Coccidioides* mats were ground with sand to release Jacobson's "endotoxin" and shaken with the broth prior to filtration. Stewart (12) prepared a coccidioidin from one year old ammonium chloride and sodium acetate liquid synthetic medium culture, ball-mill ground. Purification was by filtration through 2 per cent collodion filters. It was standardized on infected sensitized guinea pigs. This coccidioidin was used rather extensively around the San Francisco area. Other coccidioidins have been prepared but mainly used in individual cases. It may be pointed out that the material used by da Fonseca and de Arêa Leão (13) was not prepared from *Coccidioides immitis* but *Paracoccidioides braziliensis* and their observations are irrelevant.

The discoveries of Dickson (14) and of Gifford (11) of the etiology of Valley Fever launched an epidemiological study of this subject in 1937 (15). One of the requisites of the study was coccidioidin. Previously we had tried the ammonium lactate synthetic medium suggested by Hirsch, Benson and D'Andrea (4, 5) as well as the ammonium chloride-sodium acetate medium used by Stewart and Meyer (16) and which Stewart (12) used for his coccidioidin. In our hands, these synthetic media coccidioidins did not seem sufficiently potent within a reasonable time; one recalls that the Hirsch ammonium lactate cultures were incubated six months and Stewart's subsequent description gave a year incubation. With speed an essence, we first prepared an emergency coccidioidin (our Lot 1) by growing four strains of *Coccidioides* on peptic digest glucose broth for five weeks, adding merthiolate to a final concentration of 1:10,000 and then Berkefeld filtering. This material was satisfactory in the field and was the coccidioidin mentioned by Dickson (14c) when he addressed the National Tuberculosis Association on coccidioidomycosis the last time it met in California. However, we were dissatisfied with its content of foreign protein. Knowing that the asparagine synthetic medium used for tuberculin had proven to be beyond criticism as to antigenic and nonspecific characteristics, we made some preliminary tests which indicated that by reducing the glycerine content to 2.5 per cent we could use the Bureau of Animal Industry tuberculin formula (17). Our only other modification has been to substitute half (0.7 per cent) of the asparagine with ammonium

chloride. Elimination of the asparagine resulted in a very inferior product. Other constituents like the iron salts are not absolutely necessary. The zinc salts which Roessler and associates (18) have shown to be necessary in their inorganic basal medium do not enhance *Coccidioides* growth or coccidioidin production in this asparagine synthetic medium.

The medium for the coccidioidin has been prepared as follows:

1-Asparagine.....	7.0 grams
Ammonium chloride.....	7.0 "
Dipotassium phosphate C.P. ( $K_2HPO_4 \cdot 5 H_2O$ ).....	1.31 "
Sodium citrate C.P. ( $Na_2C_6H_5O_7 \cdot 5 \frac{1}{2} H_2O$ ).....	0.9 "
Magnesium sulphate U.S.P. ( $MgSO_4 \cdot 7 H_2O$ ).....	1.5 "
Ferric citrate U.S.P. VIII (Scales).....	0.3 "
Dextrose of the grade known as cerulose, U.S.P.X.....	10.0 "
Glycerine C.P. (U.S.P.).....	25.0 "
Water to make.....	1000.0 ml.

Dissolve asparagine in about 300 ml. of hot distilled water, 50°C. Dissolve each of the organic salts in 25 ml. of water, ferric citrate being dissolved in hot water. Add each salt in order, starting with ammonium chloride, to the hot asparagine solution and mix well each time the salt is added. Then add dextrose and glycerine and finally make up to volume. Fill 1500 ml. to each 2800 ml. Fernback flask. Then sterilize at 240°F for fifteen minutes.

#### THE FUNGUS USED AS INOCULUM

Theoretically, *Coccidioides immitis* strain differences might occur with resultant failure of coccidioidin to react because of antigenic variations. For this reason, frequently (3, 10) *Coccidioides* from several sources have been used as inoculum. Stewart (19) reported instances where coccidioidins appeared to be specific for the autogenous infection in animals. He suggested this possible explanation for frequent failure of patients with coccidioidal granuloma to react to coccidioidin. On the other hand, Hirsch and Benson (4) noted no significant variations in the specific coccidioidins prepared from three strains. Kessel (10b) reported no restriction to autogenous coccidioidins of guinea pig sensitivity. To provide maximal security for antigenic "coverage", we have used multiple strains. During the first two years, we used four strains; subsequently the inoculation has been with ten strains. These ten strains include *Coccidioides* from patients with disseminated infections and poor allergy, with erythema nodosum and erythema multiforme with strong allergy, with pleural effusion, with uncomplicated coccidioidal infections, with pulmonary cavity and geographically from various endemic areas. We have also included one or two strains isolated within the preceding year. In our inoculation, two loopsful of *Coccidioides* from a one to four month Sabouraud's culture of each strain have been placed in an 8 ml. tube with glass beads. Then 7 ml. sterile saline have been added and the suspension shaken two to four hours. One ml. of this suspension has been used to inoculate each flask.

To investigate possible strain differences, whenever feasible we have made an autogenous coccidioidin for clinical trial in the rare patient failing to react to stock coccidioidin. Thus far, autogenous coccidioidins have not been more effective in evoking reactions than the stock preparations.

A more systematic method also has been used to investigate possible strain variation. Strain specific coccidioidins have been prepared as follows:

In 500 ml. Erlenmeyer flasks 250 ml. of asparagine synthetic medium are autoclaved at 240°F for fifteen minutes. Each flask is inoculated with a 1.0 ml. suspension of a one to four month culture of a specific strain. It is harvested at two months by Seitz filtration and 1:1000 aqueous merthiolate is added in proportion of one part of merthiolate to 9 of coccidioidin. Sterility tests are performed.

These specific coccidioidins have been tested on the backs of 2 and sometimes 3 sensitive, previously infected persons in dilutions of 1:100, 1:1000 and 1:10,000. Fifteen to 17 coccidioidins have been tested simultaneously with readings at twenty-four and forty-eight hours. The following "strains" have been compared:

From California and Arizona patients with:

Coccidioidal granuloma	
Fatal disseminations.....	4
Nonfatal disseminations.....	2
Hydropneumothorax.....	1
Erythema nodosum.....	4
Erythema multiforme.....	3
Pulmonary cavity.....	1
Uncomplicated primary infection.....	5

From Patients elsewhere:

Weidmann (#1136 and #2322).....	2
Castellani (via Ciferri and Redaelli).....	3
("Geotrichum louisianoideum")	
("Glenospora metacuropea")	
(C. immitis var. Metacuropeus)	

From cow.....	1
From soil without passage through animal.....	1

Total..... 27

It is to be noted that the strains of *Coccidioides* have been from various geographical areas (Texas, Arizona and several endemic areas of California and even include two recovered from the Balkans and Italy).

All of these strain-specific coccidioidins caused equivalent reactions. (See figure 1.)

The possibility that an *autogenous* coccidioidin might evoke a stronger response than other coccidioidins was also tested. As we shall see, poor sensitivity and even anergy are frequently encountered in patients with coccidioidal granuloma (disseminated coccidioidal infection). Therefore, we arranged an interchange of strain specific coccidioidins to include the appropriate autogenous coccidioidin. Four tests were performed on the volar surfaces of each forearm. The recipients of the autogenous coccidioidins were two coccidioidal granuloma patients (one reacting only with a 1:10 coccidioidin and one completely anergic), two former erythema nodosum patients and two former erythema multiforme patients all four of whom reacted violently with 1:1000 dilution, and two without skin le-



sions. The highly sensitive patients reacted vigorously to all the coccidioidins used. The coccidioidal granuloma patients reacted poorly or not at all to all the strains tested. In no instance did the patient react more strongly to his own

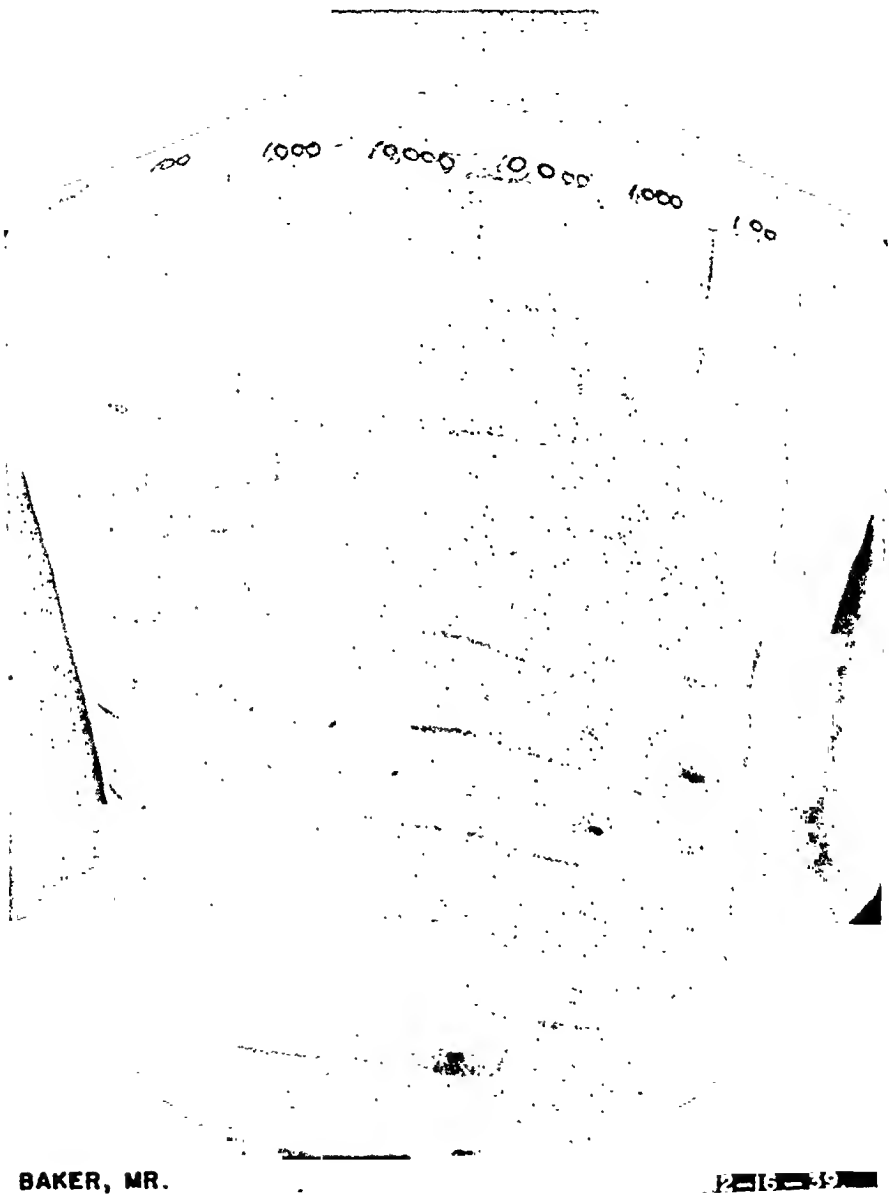


FIG. 1

autogenous material. Moreover, autogenous coccidioidin tests with the two-month "standard" method of producing the coccidioidin were tried in 5 others (all of whom had uncomplicated primary infections) and in no instance was a stronger reaction elicited than was observed for heterogenous coccidioidins.

While the possibility still exists that there may be antigenic strain variations, these must be unusual. There seems to be conformity with the morphology of the fungus itself which does not show distinctive "strain" characteristics (20). Even though the allergy of the hosts varies, the variation does not seem to be due to differences in the parasite or more appropriately, the "pathogenic saprophyte." We shall return later to the subject of sensitivity in patients with disseminated infections.

## GRINDING AND METHODS OF FILTRATION

Jacobson (6b) (presumably), Kessel (10) and Stewart and Kimura (12) all ground the fungus mat and incorporated it in the broth before final filtration. Kessel ground the mat with sand. Stewart used a Krueger ball mill. Stewart also used the 2 per cent collodion filters of Krueger. In order to evaluate the possible effect of grinding the mycelium and differences effected by filtration the following study was made.

To 1500 ml. of Stewart-Meyer (16) medium in a 2800 ml. Fernback flask the usual 1.0 ml. 10-strain-inoculum was added and the flask incubated. Two and a half months later the identical suspension which had been refrigerated in the interim was inoculated into a similar flask of our asparagine medium. Two months later the coccidioidins were harvested. The mycelial mats were weighed. The Stewart-Meyer medium mat weighed

Strain sources of the coccidioidins used in figure 1 with measurements of induration in millimeters for each dilution

STRAIN SOURCE	1:100	1:1000	1:10,000	1:10,000	1:1000	1:100	STRAIN SOURCE
1. Hydropneumothorax	10 x 20	15 x 15	3 x 3	2 x 2	10 x 12	15 x 18	9. Coccidioidal granuloma (Texas)
2. Erythema multiforme ++++ 1:1000	15 x 15	13 x 13	2 x 3	3 x 3	13 x 15	15 x 18	10. Castellani <i>Glenospora melaeuropaeus</i> (Balkans)
3. Lot 4, eight strains	15 x 18	13 x 15	4 x 4	2 x 3	14 x 16	15 x 15	11. Castellani <i>Glenospora melaeuropaeus</i> (Italy)
4. Fatal coccidioidal meningitis ++ 1:100	17 x 20	15 x 16	4 x 5	7 x 7	15 x 16	10 x 20	12. Pneumonia laboratory infection
5. Fatal coccidioidal granuloma multiple abscesses Ncg. 1:10	20 x 20	13 x 12	6 x 7	6 x 5	15 x 18	20 x 20	13. Pneumonia laboratory infection; autogenous
6. Erythema nodosum (Yolo County)	20 x 22	14 x 15	5 x 5	8 x 9	16 x 17	20 x 23	14. Fatal coccidioidal granuloma; skin, nodes. Ncg. undil.
7. Pneumonia infection	15 x 20	12 x 14	3 x 5	7 x 10	15 x 18	22 x 22	15. Fatal miliary dissemination
8. Lot 5, eight strains	20 x 25	15 x 17	5 x 5	8 x 9	17 x 17	23 x 25	18. Effusion

	1:10,000	1:1000	1:100
Bovino	4 x 5	13 x 15	20 x 25

FIG. 1. Titrations of specific coccidioidins

15 g. and the entire mat was placed in a ball mill and ground with 110 ml. of its liquid at 45 R.P.M. for twenty-four hours. The asparagine medium mycelial mat weighed 86 g. and 15 g. were removed and ground with 110 ml. of the liquid for twenty-four hours. Half of the ball-mill grind was filtered through Berkefeld filters and half through collodion filters<sup>4</sup>. Each kind of liquid medium without mat was filtered through Berkefeld candles and Krueger collodion membranes. Thus we had the ammonium chloride-sodium acetate and the asparagine synthetic medium coccidioidins both with and without mycelial mat ground with them, each subjected to filtration through Berkefeld candles or collodion membranes. Three sensitive people were tested simultaneously with these 8 coccidioidins in 1:100, 1:1000 and 1:10,000 dilutions. All 4 of the ammonium chloride-sodium acetate preparations produced reactions of similar size. The same was true for the asparagine medium coccidioidins. However, the asparagine medium coccidioidins were over ten times more potent than the ammonium chloride-sodium acetate coccidioidins.

These results indicate that neither grinding the mycelium in the broth nor substituting 2 per cent collodion membranes for Berkefeld candles in filtration affect the potency of coccidioidin. However, asparagine synthetic medium in two months produces a coccidioidin over ten times the strength of coccidioidin from four and a half month old ammonium chloride-sodium acetate medium.

#### HEAT STABILITY OF COCCIDIOIDIN AND CONCENTRATION OVER WATER BATH

Coccidioidin is extremely stable. Hirsch and Benson (4) indicated that heating at 60° to 80°C. for thirty minutes did not reduce its potency. The coccidioidins of Beck (7) and Kessel (10a) were autoclaved. The coccidioidin prepared by Eddie (9) was also heat killed. Stewart and Kimura (12) reported that their coccidioidin as well as that prepared by Eddie, Jacobson and our Stanford workers withstood autoclaving for thirty minutes at 15 pounds pressure. Our studies on this heat stability had been carried out prior to our knowledge of Stewart's experiments and while they agree in general there are a few variations and additional aspects.

One lot consisting of two flasks (3000 mls.) of asparagine medium inoculated with the usual 10 strains was harvested after two months of incubation. The fungus mat was separated, washed and found to weigh 120 g. Then proportionate parts (9.1 g.) of mycelial mat were restored to each of two 225 ml. portions of unfiltered liquid culture. The remainder of the coccidioidin was Berkefeld filtered and aqueous 1:100 merthiolate added in the proportion of one part to 9 of coccidioidin. Then 50 ml. portions of this final product were removed and heated with the reconstituted material. Moreover, after washing, equivalent weights (9.1 g.) of washed mycelial mat were placed in 225 ml. of Coca's (21) extracting fluid and in 225 ml. of distilled water. Thus coccidioidin completely prepared, unfiltered asparagine broth culture with mat, mat in Coca's solution and mat in distilled water were simultaneously autoclaved at 250°F for ten min-

<sup>4</sup> Filters were kindly supplied by Dr. Albert P. Krueger, Professor of Bacteriology, University of California.

utes. Four similar preparations were kept in streaming steam for one hour. The Coca's solution and distilled water suspension and the reconstituted asparagine medium culture were then Berkefeld filtered and one-ninth part of aqueous 1:1000 merthiolate was added. Then 200 ml. of the filtrates of the two distilled water suspensions, of the reconstituted coccidioidin with mat and of the regular coccidioidin were each concentrated to 20 ml. over a water bath. The materials were tested simultaneously on the backs of 2 previously infected and known sensitive persons together with the untreated coccidioidin of the same lot in 1:10,000, 1:1000 and 1:100 dilutions. There was a slight reduction, possibly one-fifth, in the reactivity of all of the heated materials. There was no difference when mycelium was heated in the medium. Moreover, the Coca's solutions in which the washed mycelia were heated had the same potency as did the heated coccidioidins. The concentration to one-tenth volume yielded a product which was simply the equivalent of the unconcentrated material; i.e., the reduction in volume had not yielded a product ten times as potent. These results do bespeak an exceedingly stable active principle. However, because we feared a qualitative reduction in active principle might interfere with its diagnostic value, we continued to harvest our coccidioidin without heating it.

#### POTENCY AND SPECIFICITY

When relatively small amounts of coccidioidin are made, we have already seen that the resulting coccidioidins are very similar in potency. With our initial coccidioidins we were blissfully ignorant of any possible variations in potency. Fortunately we always compared new lots of coccidioidin by making serial dilutions and trying the new coccidioidin and the old in 3 or 4 of us who had been infected around the laboratory and who were sensitive. As the demand for coccidioidin was quite modest until we embarked on our Army work, only a few lots of coccidioidin were used by us or distributed to other experimenters. However, the military demands made necessary many additional lots of coccidioidin. In this larger scale production we began having whole batches which were inferior. Despite the fact that we would use the same multiple strain inoculum in medium made identically, incubated in the same incubator and placed in the identical place in the incubator, we found as much as five fold difference in potency. A comparable problem is well known with tuberculin and has recently been reviewed by Holm (22). We first attempted potency determinations on infected albino guinea pigs. An ingenious elaboration of this method of standardization was proposed by Stewart and Kimura (12). They suggested determining a minimal reacting dosage in sensitive guinea pigs and then using one hundred times that amount in the 0.1 ml. human intracutaneous test. We found that infected guinea pigs varied greatly in sensitivity. Frequently we would get one reacting to 1:10 dilution and occasionally one reacting to 1:100 or 1:1000 dilution. However, undiluted coccidioidin was necessary to evoke dependable reactions in them. Therefore, it appears difficult to set up standards such as are used for diphtheria toxin and suggested by Stewart. While a preliminary test of potency can be

made on laboratory animals, humans seem necessary for final comparisons. Again the comparability to tuberculin standardization is apparent. A difference in the nonspecific reactions of various lots of coccidioidin makes even more important final checking in man.

The specificity of coccidioidin has been widely discussed. One of the early questions (7) was the possible cross reaction with tuberculin. The frequency of coccidioidal sensitivity in the general population, but especially their tuberculous cases, made the Hurwitz group (9) question specificity. As a matter of fact, the coccidioidin they used was in the equivalent of a 1:10 dilution and might well have had some nonspecific reactions. More importantly, however, residence histories were not taken and the long duration of sensitivity not appreciated. Kessel's series (10) taking into account residence bore out the specificity of the coccidioidin with respect to tuberculous humans and his careful experimental studies in guinea pigs gave additional evidence against cross reaction with tuberculosis. However, Aronson (23) provided the clinching proof that there is no cross reaction of coccidioidin in the tuberculous. Among Alaskan Indians in whom 96 per cent reacted to tuberculin none reacted to 1:100 coccidioidin and only 3 (1.1 per cent) to 1:10 coccidioidin. On the other hand, there was very significant cross reaction between tuberculin and *Br. abortus* protein. In South Dakota Indians with no reaction to coccidioidin, two-thirds reacted to tuberculin and heteroallergic reactions were demonstrated to the proteins of *M. smegmatis*, *M. ranae* and *M. marinum*. Finally, Arizona Indians in the northern part where 84 per cent were tuberculin positive were only 15 per cent coccidioidin reactors and with these history of exposure in the highly endemic southern Arizona area could generally be elicited. In the Pima Agency with 84 per cent coccidioidin reactivity tuberculin sensitivity was seen in 37 per cent. Moreover, the age distribution of coccidioidin sensitivity did not follow the pattern of tuberculin sensitivity.

That cross reactions do occur was suggested to us by the unpublished studies of Nelson and Furcolow (24) in Ohio where a very considerable number of children reacted to coccidioidin, especially in the stronger concentrations. We were unable to reconcile these findings with the reports of other investigators (23, 25) and with our own experience in Northern California where it was practically always possible to unravel an association between a reactor and a coccidioidal endemic area. However, in 1941 we began our Army studies and the coccidioidin skin testing of personnel from all over the United States. We found occasional unequivocal reactions and a considerable number of equivocal reactions in personnel whom we would test immediately on their detraining and who never before had been west of the Mississippi River. Accordingly, in 1943 (26) we called attention to these reactions, indicating the importance of carefully evaluating the significance of the coccidioidin reactions in persons from the Middle West (and we would also now add, the South). Cross reaction with another fungus was suggested with *Histoplasma* as one possibility. Aronson (23) had found suspicious reactions to histoplasmin in some of the coccidioidin sensitive Arizona Indians and Emmons (27) reported even more reactions to haplosporangin in these coc-

coccidioidin reactors. However, our problem was the reverse, the possibility of coccidioidin reacting to infections other than coccidioidomycosis.

Fortunately, our Lot 9 coccidioidin which Aronson and Emmons both had used gave minimal nonspecific reactions. Throughout our entire Army studies we used this same Lot. When coccidioidin in 1 to 100 dilution was used, only rarely were these "nonspecific" reactions 5 mm. in diameter. However, when 1:10 was used, many were frankly positive (induration of 5 mm.). In other lots we found great variability. In no instance was the specificity better than with Lot 9. Generally the degree of nonspecific reaction paralleled potency. However, sometimes with potency less than or no more than equivalent to that of Lot 9, a new lot of coccidioidin gave a greater proportion of these nonspecific reactions. With longer incubation the tendency to nonspecificity increased rapidly. We attempted to eliminate the undesirable quality by concentrating ten fold behind 13 per cent collodion ultra filters as described by Seibert (28) and first used by Henderson (29) for coccidioidin. We then added merthiolated buffered saline to make back to the original volume, sampled the material and repeated the process four times. Each time we concentrated, we lost approximately 10 per cent of the active principle. The product of four "washings" had between one-half and two-thirds its original potency and when we allowed for this in making up our dilutions the nonspecific factor seemed undiminished. Even in the "polysaccharide" prepared by Baker (30), the nonspecific quality appeared to be no different than in the coccidioidin from which it was prepared.

In harvesting our coccidioidin we adopted the plan of sampling the coccidioidin at six weeks. To 45 ml. of the sample 5 ml. of aqueous 1:1000 merthiolate would be added and then Seitz filtered. This material would be tested on one of us in comparison with Lot 9. If it appeared to be potent, it would be taken on the next week's trip to a San Joaquin Valley Air Field and tried on several coccidioidal patients. If it did not seem adequate, incubation was continued with sampling at weekly intervals. As soon as the potency seemed adequate, the coccidioidin was harvested. Sometimes even after ten weeks of incubation the material was still not the equivalent of Lot 9. Then it could be concentrated behind the collodion filters to an appropriate strength. To each flask of 1500 ml., 150 ml. of aqueous 1:1000 merthiolate were added. This addition brought volume practically back to the 1500 ml. mark which we made at the time of inoculating. Then the material was Berkefeld filtered, sterility tests were performed and a preliminary test made on one of us. One might have titrated by taking several sensitive persons and comparing varying dilutions of our standard Lot 9 and the new lot. However, we combined the final potency tests with the necessary specificity determinations. When we were at the air fields coccidioidin testing the new arrivals (31) with 1:100 Lot 9 coccidioidin, we gave a second intracutaneous test with a 1:100 dilution of the new lot in an adjoining area of the volar surface of the forearm. The readings were compared. With the residence histories known, we could evaluate the results and determine potency and specificity. An example is given below. Lot 29 and Lot 31 both of which were slightly under the potency of

Lot 9 were pooled and concentrated two fold. After Berkefeld filtration and sterility tests, the new Lot 29-31 was tested on March 4, 1945 at Merced A.A.F. and on March 27, 1945 at Minter Field. The results showed:

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Both negative..... 182

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Both $\pm$ .....	12	"Nonspecific" group, residence in middle western and southern states. Total 18.
Lot 9 $\pm$ ; Lot 29-31 negative.....	5	
Lot 9 negative; Lot 29-31 $\pm$ .....	1	

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Both +.....	7	All either current coccidioid patients or long time residents of the San Joaquin Valley, Arizona or West Texas. Total 24.
Both ++.....	8	
Lot 9 +++; Lot 29-31 ++.....	1	
Both +++.....	7	
Both ++++.....	1	

---

The size of reaction indicated by symbols is the generally accepted one of:

- $\pm$  induration with diameter under 5 mm. or redness without induration,
- + induration with diameter of 5 to 9 mm.,
- ++ induration with diameter of 10 to 19 mm.,
- +++ induration with diameter 20 mm. or over,
- ++++ necrosis, which in our experience occurs only with reactions at least 20 mm. in diameter.

The new Lot 29-31 was then judged the equivalent of Lot 9 in specificity and potency. Incidentally, it is the lot currently being used.

The coccidioidin has not been distributed commercially and is for experimental use only. Its distribution was first made possible by the Rosenberg Foundation and for the past six years by the Army Epidemiological Board. The standardized coccidioidin has been used in numerous surveys and studies (15, 23, 25-27, 31-51).

#### TUBERCULIN TYPE OF SENSITIVITY

The delayed type of coccidioidin reaction is similar to that of tuberculin. An "immediate" type of reaction is also encountered as was emphasized by Hirsch (4, 5a,b). However, we also observed "immediate" reactions (a wheal with pseudopods developing within fifteen minutes to an hour) in persons who failed to develop a "delayed" type reaction and who were too recently in the endemic area to have acquired infections and lost sensitivity. Moreover, we elicited similar reactions with sterile distilled water. In two very sensitive persons we have seen generalized urticaria occur eight to eighteen hours after the coccidioidin test. One was a patient still undergoing his infection and another was seen at retest time without evidence of current infection. These may well have been coincidental.

In some instances the "delayed" type of reaction begins to appear in six hours and is nearly always discernible in twenty-four hours. The peak is usually around thirty-six hours. The reaction is generally still present and sometimes maximally so at forty-eight hours. If one reads at twenty-four hours, some slow

reactions may be missed, while at forty-eight hours some may have waned or even vanished. We tested one person who was negative at forty-eight hours but whose reaction began at seventy-two hours and by ninety-six hours when we saw him again measured over 3 cm. in diameter. He was not simply developing sensitivity as he was a long-time resident of endemic areas, was symptomless and his sedimentation rate and X-ray films were normal. However, as with tuberculin tests, either a twenty-four or forty-eight hour reading will usually detect positive reactions.

These characteristics would make improbable any passive transfer of sensitivity. In 1939 attempts at passive transfer combined with coccidioidin "neutralization" of serum from infected sensitive guinea pigs were failures, although precipitins were demonstrable and those observations started us on our serological testing. Because of the inferior sensitivity of guinea pigs, in 1944 a restudy of the

TABLE 1

*Immunological status of 5 serum donors in passive transfer tests of coccidioidin sensitivity*

CASE	CLINICAL STATUS COCCIDIOIDOMYCOSIS	NUMBER OF DAYS SINCE ONSET		CURRENT COCCIDIOIDIN SENSITIVITY (1:100 DI.L)	PRECIPITINS		COMPLEMENT FIXATION	
		Cocci-dioide-mycosis	Erythema nodosum		Previous	Current	Previous	Current
P.	Recovered	161	None	+++	++++	0	++++	++++
M.	Recovered	130	113	++++	++++	0	++++	0
B.	Convalescent	71	None	++	++++	++++	++++	++++
Cu.	Active	11	None	+++	No test	++++	No test	0*
Ch.	Active	0	4 (Current)	++++	No test	++++	No test	0

\* Complement fixation tests were positive the following week.

situation was carried out using the facilities of the Lemoore A.A.F. Station Hospital allergy clinic. The donors were 5 current or recovered coccidioidal patients with good sensitivity. Their immunological status is presented in table 1.

The Prausnitz-Küstner passive transfer tests were performed according to the usual technique as described by Walzer (52). Serum from each of the 5 donors was collected and separated aseptically. Three coccidioidin negative recipients each received 0.1 ml. of each serum intracutaneously in each site to be tested. Seventy-two hours and one week later each site was tested with 0.1 ml. freshly diluted 1:100 Lot 9 coccidioidin. No reactions developed. The recipients were tested one week later and were still negative to coccidioidin.

#### DEVELOPMENT OF SENSITIVITY TO COCCIDIOIDIN

The time of development of allergy after coccidioidal infection is acquired is of importance since not infrequently the coccidioidin test is performed before sensitivity has developed. Then one may feel the diagnosis has been eliminated when in reality he has laid the foundation for the most sensitive method of diagnosing



infection, the change from no reaction to a reaction. One should recall that the incubation period is generally from ten days to two weeks with a range of seven to twenty-eight days (15, 36, 38). When we list the time for development of coccidioidin sensitivity, we are relating it to clinical onset. Also we should recall that 60 per cent of the coccidioidal infections are completely inapparent (32).

Previously we had noted that coccidioidin sensitivity is established within two days to three weeks after onset (15). Sweigert (51) using 1:1000 coccidioidin noted that 11 of his clinical cases were coccidioidin negative on admission and did not become positive until two to three weeks later. Willett (44) had one patient who did not become positive for six weeks. In our present series, excluding those who disseminated, all reacted. We had one patient who had been negative only two and one-half months before he gave a ++ reaction. He denied any symptoms whatsoever. Although his serological tests were negative, his sedimentation rate was 20 mm. (Cutler method). He was classed as an "inapparent infection." Then five days later he suddenly developed pleural pain, malaise, fever, headache, cough and all the other symptoms of a moderately severe coccidioidal infection. Precipitins and complement fixing antibodies were demonstrable in his serum and the roentgenogram showed a lesion in his left lower lobe. His sedimentation rate remained elevated for sixty days and he required seventy days of hospitalization. One of our 4 coccidioidal erythema nodosum patients who had no symptoms prior to the erythema nodosum developed pleural pain and cough three days after his erythema nodosum. His "allergic phase" preceded his acute respiratory symptoms. However, as has been indicated, the really confusing problem comes when the initial test is negative.

Of 462 clinical cases of nonprogressive coccidioidal disease, 77 or one-eighth were negative when tested with 1:100 coccidioidin during the first week of illness. Of the 274 not previously positive, tested during the second week of illness, 19 or 6.7 per cent were negative. Only one or 1 per cent of 101 with an initial test later than the second week was negative. He was negative on the sixteenth day of his illness but positive subsequently. The subsequent positive tests establishing the diagnosis were made at variable times. However, approximately one-half were found to be positive within a week. The fact that we used only 1:100 dilution and not 1:1000 probably accounts for the more rapid recognition of the coccidioidin sensitivity than was noted by Sweigert.

It would have been interesting to have tested with both 1:100 and 1:1000 simultaneously and definitely establish whether those initially negative to 1:1000 dilution reacted to 1:100. However, we feared that there would be confusion in the bottles. We did retest more than one hundred reacting patients, some as many as four times. A progressive development of sensitivity was demonstrable in those tested in the first ten days and who had small reactions. Beare (46) called attention to this increasing sensitivity among his Air Force patients. Concise presentation of this progression in retested patients is impossible. However, figure 2 clearly shows this same type of increasing sensitivity. During the first week nearly half the reactions were only +, while combined + and ++ reactions comprised 71 per cent. During the second week there were approximately the

same proportion with reactions ++ or under as with +++ or over. In the third week only one-quarter had reactions of ++ or less. After the third week one-sixth had + and ++ reactions (less than 2 per cent with + reactions) while five-sixths had reactions measuring 20 mm. or over. One-third developed actual necrosis.

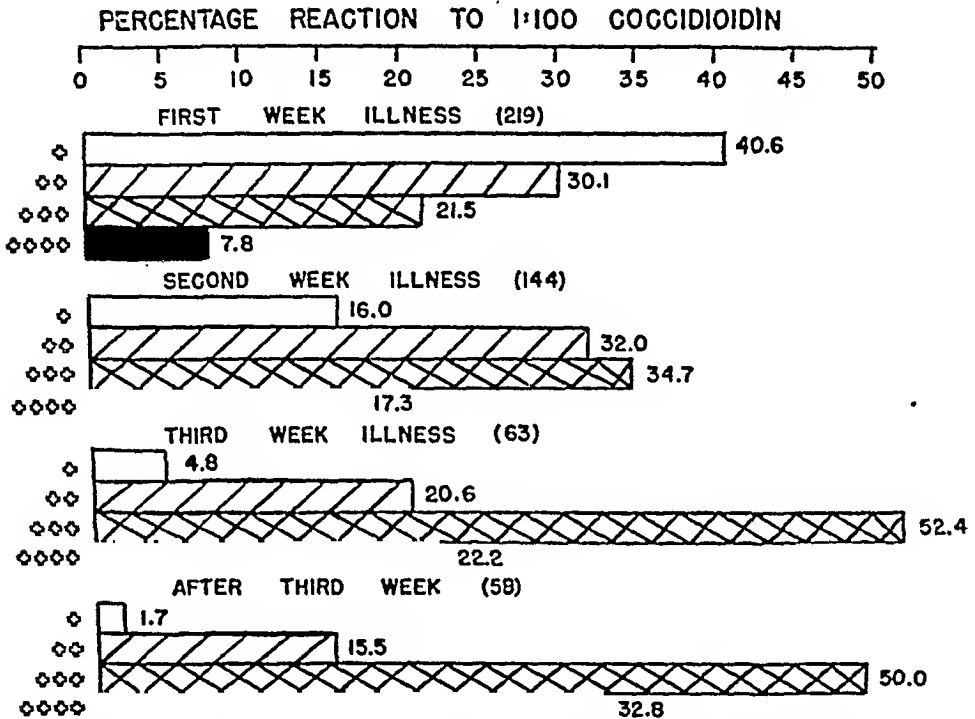


FIG. 2. Distribution of reactions in 484 patients having nondisseminating coccidioidal disease by week of illness. San Joaquin Valley Air Fields 1941-1946.

#### RELATION TO ERYTHEMA NODOSUM

The true "Valley Fever" of Gifford and Dickson, coccidioidal erythema nodosum, is associated with very strong sensitivity to coccidioidin. Gifford first (11a) and then Dickson (14b,c) indicated the hypersensitivity association. Kessel (10a) reported a convalescing "Valley Fever" patient who had recurrence of symptoms after a repetition of the coccidioidin test. Our previous study (15) showing the association of coccidioidal erythema nodosum with coccidioidin sensitivity has been extended considerably. On a number of occasions we saw the erythema nodosum lesions exacerbate at the time of a vigorous coccidioidin reaction. In four instances, coccidioidin skin tests which caused severe local reactions also precipitated erythema nodosum. Our first experience was with a very cooperative young man convalescing from an attack of primary coccidioidal infection acquired in the San Joaquin Valley oil fields. Forty-four days after his onset, still feeling asthenic, he reported for a check-up while we were testing sev-

eral batches of coccidioidin including some which had been carried in the car in the San Joaquin Valley for two years. We had expected deterioration in potency and on ourselves and the patient used 1:100 and 1:1000 dilutions of the two coccidioidins in question and a 1:1000 dilution of our current lot. The next day he reported in with violent reactions, ++++ even to the three 1:1000 dilutions, and had typical erythema nodosum lesions over the anterior tibial and gluteal regions. New erythema nodosum lesions continued to appear for four days. However, otherwise his clinical recovery was not interrupted. A week later he felt well. In the Army Air Field studies one patient with a + reaction at eleven

TABLE 2

*Interval between positive coccidioidin test and coccidioidal erythema nodosum by duration of symptoms*

San Joaquin Valley Air Fields 1941-1946

NUMBER OF DAYS BETWEEN COCCIDIOIDIN TEST AND ERYTHEMA NODOSUM		DAY OF ILLNESS ON WHICH ERYTHEMA NODOSUM OCCURRED			ALL
		1-7	8-14	>14	
Same day.....		7	3	1	11
1 day	Before ery. nod.....	9	7	3	19
	After ery. nod.....	0	5	1	6
2 days	Before ery. nod.....	6	4	3	13
	After ery. nod.....	3	3	1	7
3 days	Before ery. nod.....	1	2	2	5
	After ery. nod.....	3	4	1	8
4 days	Before ery. nod.....	1	1	1	3
	After ery. nod.....	1	2	0	3
Over 4 days	Before ery. nod.....	2	20	12	34
	After ery. nod.....	7	9	7	23
All.....		40	60	32	132

days was retested at twenty-seven days and along with his ++++ reaction, on the following day he developed erythema nodosum. Another patient showed a ++ reaction on the seventh day. We retested her on the fortieth day of her illness and the following day she had a ++++ reaction and erythema multiforme. We had only one patient in whom we caused erythema nodosum by the routine testing. This patient developed erythema nodosum the day after his test, which was ++++. He was shown to have a lesion in his left lower lobe, precipitins, complement fixation and a rapid sedimentation rate. He gave a history that sixty-two days before his test he had pleural pain, cough, malaise, anorexia, headache, nightsweats and fever lasting a week. However, the mere fact of a severe coccidioidin reaction does not explain the occurrence of the erythema nodo-

sum. In the thousands of coccidioidal reactions evoked in our routine testing, never did erythema nodosum occur in a patient who was an old reactor and only this once did we produce it in a "change-over." One must conclude, then, that the precipitating effect will be seen only in a still active, "unstable" infection.

There seemed some indication that during coccidioidal disease, if the person was highly sensitive, the skin test *per se* precipitated erythema nodosum. It should be reemphasized that *all* these patients reacted strongly to coccidioidin. In table 2 we see an apparent disproportionately large number of patients were skin tested the *day* of the erythema nodosum since the appearance of the erythema nodosum either alarmed them into coming to sick call or, if the lesions occurred in a patient under care, alerted the physician to the diagnosis. Especially do we note the concentration of the coccidioidin tests one and two days prior to erythema nodosum when the erythema nodosum occurred in the first week of illness. It may be observed that of the 132 cases of erythema nodosum 30 per cent occurred in the first week, 46 per cent in the second, 20 per cent in the third and 4 per cent later. Two of the latter 6 were indicated as having followed promptly after the coccidioidin test. Perhaps some of those occurring in the first week occurred earlier because of the skin test performed at that time.

We may be certain, then, that if the patient's erythema nodosum is coccidioidal he will react to coccidioidin. On the other hand, not even in coccidioidal endemic areas are *all* cases of erythema nodosum coccidioidal. In a previous study (15) of erythema nodosum in the San Joaquin Valley, we found approximately 5 per cent not to be coccidioidal. Also during the Army studies we occasionally observed other causes. Having a record of coccidioidin reaction of the soldiers was very helpful in working out the etiology.

#### DURATION OF COCCIDIOIDIN SENSITIVITY

Obviously, the duration of sensitivity to coccidioidin is very important in interpreting the significance of a positive skin test. From the fact that susceptible persons may be infected at rates exceeding 25 to 50 per cent per year, one perceives that in highly endemic areas sensitivity is rapidly acquired. That the sensitivity persists is shown by the fact that 80 to 90 per cent of long-time residents react. However, the point has been raised that the sensitivity may be maintained by continued repeated exposures. This objection would invalidate the evidence (15) for durability of sensitivity where it was shown that patients in the highly endemic upper San Joaquin Valley who gave a history of erythema nodosum five to twenty-one years before still reacted vigorously to coccidioidin. However, one other "Valley Fever" patient was tested nine years after his laboratory infection. His last possible coccidioidal exposure had been six years before, yet he gave a ++++ reaction to 1:1000 coccidioidin. During the years we have accumulated instances of scores of persons who retained coccidioidin sensitivity four to ten years after leaving coccidioidal areas and of 9 who had been away from possible exposure over twenty years. However, these might well be exceptions. Aronson and Gallagher (35) retested pupils at the Phillips Academy in Massachusetts who had reacted to Lot 9 1:100 coccidioidin three months previously.

Seven reactors tested the same, 5 showed smaller and 3 larger reactions. These variations might well occur in skin testing without alteration in sensitivity. On the other hand, Cheney and Denenholz (43) described very rapid loss in coccidioidin sensitivity. For instance, of 11 patients reacting to coccidioidin on arrival at Hammond General Hospital, 5 had become negative by six months, and 9 by eight months. Of the two still reacting, one had dropped from +++ to ++ and the other from ++++ to ++, while at nine months he was down to +. Their studies also indicated that Modesto in the northern San Joaquin Valley was not an important endemic area. They noted apparently rapid loss of sensitivity in persons known to have retained sensitivity while in endemic areas, which again suggested the possibility of restimulation by reexposures.

Fortunately, an opportunity to recheck the duration of sensitivity was provided in our coccidioidal control program (31, 32). Nonreactors were retested every six to twelve months. We had excused those once positive from the semi-annual retest. Not infrequently they were retested by mistake and invariably were positive. Minter, Gardner and Lemoore Fields were all in endemic areas and did not meet the requirements of such a study because of possible reexposures. However, Merced A.A.F. had proven to be relatively free from infection and was comparable to Hammond General Hospital less than fifty miles away. During the year February 1943 to February 1944 the Merced infection rate per 100 susceptible persons was only 0.36 per cent (31) and 3 of the 5 who were infected had taken frequent trips into the highly endemic southern San Joaquin Valley. Thus only persistence of sensitivity could account for sensitivity elicited at retesting. In the February 1944 retesting we simply failed to exclude previous reactors. Seventy-eight or approximately one-third of those previously coccidioidin positive permitted retests. It was thought that those with weaker reactions would be less likely to object and more willing to permit the retest. It is to be recalled that all tests were made with 1:100 dilution of Lot 9 coccidioidin. The tests and readings were done by the same person. One condition only was altered. The retest readings were at forty-eight hours, while at Merced the initial readings were at twenty-four hours. Table 3 presents these findings. Of the 78 reactors only 2 were negative at retest and one of these when rechecked with 1:10 and 1:100 coccidioidin on a subsequent trip showed a reaction measuring 35 mm. with 1:10 and 9 mm. with 1:100 dilutions. The other had had a borderline positive reaction when originally tested, noted as "+(±)". He had been on the Field six months. It is to be noted that 69 of the 78 had been on the Field one year or longer. Forty-three had the same reading at retest, 12 had smaller and 22 larger readings. The fact that the retest readings were at forty-eight hours probably explains the excess of increase over decrease in reaction.

We have no explanation for this divergence of results. We did have the opportunity of rechecking one patient at Gardner Field who had been sent to Hammond General Hospital with a coccidioidal pulmonary cavity discovered in our routine semi-annual coccidioidin retest when his coccidioidin reaction changed from negative to +++. During his ten-month-stay at Hammond his sensitivity was reported to have regressed to faintly positive, but when we retested him fifteen months after his return to Gardner Field again we obtained +++. Both his

original tests and retest at Gardner Field were performed by and read by the same individual. The coccidioidin was from the same lot and diluted in the same manner by the same individual. Possibly this may account for more uniformity.

We do not claim that sensitivity to coccidioidin is not lost. This regression is well recognized in tuberculin sensitivity. Indeed, in early 1938, 1:10,000 coccidioidin produced a reaction of 1.0 cm. in one of us. Now in 1947 a 1:10 dilution or 0.3 ml. of 1:100 dilution are required to produce a readable reaction. However, this has occurred despite a very constant exposure to an environment of *Coccidioides immitis*, both in the San Joaquin Valley and in the laboratory. Recently, he scraped a series of dry Petri dish cultures of *Coccidioides* to harvest

TABLE 3

Duration of coccidioidin sensitivity in personnel of Merced A.A.F. with comparison of size of initial and retest reactions February 1944

SIZE OF REACTION		INTERVAL BETWEEN INITIAL TEST AND RETEST							TOTAL
Initial Test	Retest	2 yr.	1 yr. 8 mo.	1 yr. 4 mo.	1 yr.	8 mo.	6 mo.	2 mo.	
++++	++++ +++ ++		1	5 4 1	1				6 5 1 } 12
+++	++++ +++ ++	1	2 1	2 12 3	1 3				5 17 3 } 25
++	++++ +++ ++ +	1		2 3 5 2	1 1 1		1	2	4 6 7 2 } 19
+	+++ ++ + 0	1	1 3	4 7		1 1		1 1 1	1 6 14 1 } 22
Total.....		3	8	50	8	2	3	4	78

chlamydo spores. No mask was worn. Two coccidioidin-negative, normal guinea pigs with negative coccidioidal serology were placed in a basket several feet farther away from this operation than was his face. Both guinea pigs developed sensitivity to coccidioidin and a very high titer of complement fixation. When one was accidentally killed in bleeding for the serum, its lungs showed a score of large coccidioidal lesions. The coccidioidin reaction of the exposed worker has continued at the same low level and his serum is still used as a negative serum control in serological tests. Again one case is not conclusive but other evidence pointing toward persistence of immunity would also tend to invalidate the theory that sensitivity is maintained by continued exposure.

The relative persistence of coccidioidin sensitivity is in line with the findings of

Cox and Smith (54). However, Butt's (45) close correlation of autopsy findings with coccidioidin sensitivity provides the anatomical explanation compatible with analogy to the persistence of tuberculin sensitivity. He discovered healed calcified lesions in the lungs of all coccidioidin reactors (most of whom did not react to tuberculin) with spherules containing diagnostic endospores in 45 per cent and an additional 28 per cent with spherules without endospores. He found one person having a negative coccidioidin test with a pulmonary scar which contained a spherule resembling *Coccidioides* but without endospores.

#### THE COCCIDIOIDIN TEST IN DISSEMINATED COCCIDIOIDAL INFECTION

Patients with disseminated coccidioidal disease (coccidioidal granuloma) frequently react feebly or not at all to coccidioidin. This fact often results in missed diagnoses. Also, it has been responsible for some doubts (9, 19) as to the antigenic "group" coverage of coccidioidin. Gifford (11a) by noting the advisability of diluting coccidioidin in detecting benign infections, inferred a lower sensitivity in coccidioidal granuloma patients. Dickson (14) specifically alluded to this point in his pioneer papers. The large dosage characteristically required for coccidioidal granuloma patients is epitomized by Jacobson's (6) advice to use 0.3 ml. of undiluted coccidioidin. One recalls that he had established the diagnostic importance of coccidioidin but all his cases were of progressive disease. Subsequent reports (33, 39, 41, 44, 47, 48, 51) have provided ample substantiation of the low level of sensitivity to coccidioidin usually encountered in disseminated, progressive disease.

We have had a total of 100 patients who were tested while dissemination was in progress. Of this group 30 reacted to 1:100 (or more dilute) coccidioidin and 70 were not sensitive to 1:100 dilution. Of the 78 whose sensitivity to 1:10 coccidioidin was known, 30 or 39 per cent did not react. Five of the 6 in the latter group were negative even to 0.1 ml. undiluted coccidioidin. Thus coccidioidin has serious limitations in the diagnosis of disseminated disease.

However, the coccidioidin sensitivity does have important prognostic connotations. As we shall see, disseminations can occur in patients with high degree of sensitivity. If the sensitivity is maintained, the outlook is more favorable. Table 4 indicates that three-quarters of the patients who continue to react to 1:100 coccidioidin will survive, while only one-sixth of those negative to this dilution recover. With 1:10 coccidioidin, approximately one-half who continue sensitive recover while only one-tenth of the nonreactors survive. One category warrants special attention. Frequently, patients with the extrapulmonary lesion confined to the meninges retain a strong sensitivity. One should not entertain false hopes for such a patient. We have had patients reacting +++ and ++++ to coccidioidin during their meningitis but the outlook for them is well-nigh hopeless. Sweigert (51) has reported the only recovery of a patient with coccidioidal meningitis known to us. His patient reacted + to 1:100 coccidioidin. With meningitis occurring during miliary dissemination, the reaction is generally negative.

The cause of the poor sensitivity could be either desensitization by excessive

amounts of circulating antigen or inability of the body to react to *any* cutaneous stimulation. We have records of a few coccidioidal granuloma patients with tuberculin tests which indicate possibility of either explanation. Supporting the specific desensitization theory, we had 2 patients negative to 1:100 and 4 more negative to 1:10 coccidioidin who at the same time reacted to 1:1000 tuberculin. Others had earlier tuberculin tests which were positive but did not have the test repeated when the coccidioidin sensitivity waned. The theory that the capacity to react to all stimuli is depressed might be inferred from failure of 12 adult patients to react to either agent. One patient dying of a mixed coccidioidal and tuberculous infection with both organisms in the sputum reacted to neither material. This patient may have been desensitized by both organisms. However, one other patient certainly lost his general reactive capacity. During his initial coccidioidal illness, this patient was found to react ++ to 1:100 coccidioidin and +++ to 1:1000 Old Tuberculin. He disseminated two weeks later. When

TABLE 4

*Fate of patients with disseminated coccidioidomycosis according to level of known minimal coccidioidin sensitivity*

FATE OF PATIENT	MINIMAL KNOWN COCCIDIOIDIN SENSITIVITY							
	1:100 dilution				1:10 dilution			
	Positive		Negative		Positive		Negative	
	Number	%	Number	%	Number	%	Number	%
Recovery.....	15	75	11	17	19	54	3	10
Death.....	5	25	52	83	16	46	26	90
Total fate known....	20	100	63	100	35	100	29	100

retested four weeks after the dissemination, he was negative to both. He died two weeks later.

It was also our hope to determine whether dissemination ensued as the result of inability to establish sensitivity or whether poor sensitivity resulted from the dissemination. Again no definite answer can be given. Clark (47) reported 2 patients originally positive who became negative during their dissemination. We have had 11 patients who prior to evidence of dissemination responded to 1:100 coccidioidin with ++++ or +++ reactions. Six of them died. Two were never retested after dissemination. One dropped to + after dissemination while 8 became negative to the 1:100 dilution. Five of these 8 were retested with 1:10 coccidioidin and found to be negative, and 2 of the latter failed to react even with undiluted coccidioidin. A number of others who were coccidioidin-tested during dissemination showed progressive loss of sensitivity. Thus strong sensitivity does not eliminate the possibility of dissemination. Neither does a low level of sensitivity protect. We had 7 patients who repeatedly were tested with 1:100 coccidioidin early in their illnesses, and, like Sweigert's (51) 3 patients, never established sensitivity to this concentration of coccidioidin prior to dissemi-



nation. Two others had only + reactions to 1:100 coccidioidin prior to dissemination. Six of these 9 died. Two of 3 who recovered were retested after recovery and showed +++ reactions to 1:100 coccidioidin.

Establishment or reestablishment of sensitivity during convalescence or after recovery from dissemination has been noted six times. The instances are few, since rarely are the coccidioidin tests repeated. However, Dr. J. W. Burks (55) of New Orleans had a patient with proven cutaneous dissemination who was negative to 1:100 coccidioidin during his dissemination but who reacted ++++ to the same dilution coincidental with clinical improvement. Dr. Leslie B. Smith (56) of Phoenix, Arizona had a patient with proven lymph node dissemination. He has followed the post-dissemination sensitivity to 1:100 coccidioidin from no reaction progressively to ++++ sensitivity as the patient has controlled the infection. One of our veterans with extensive dissemination was negative to 1:10 coccidioidin but four and a half years later, when all his lesions had healed, his sedimentation rate was normal and his complement fixation titer had waned, he reacted +++ (41 x 41 mm.) to 1:100 coccidioidin. We also followed the coccidioidin sensitivity of 3 other servicemen prior to and during dissemination and after recovery. One patient failed to react to 1:100 coccidioidin on the third, fifth, twelfth, forty-fifth and seventy-eighth day of his illness. His dissemination occurred during the second month of illness. At the end of the third month of his illness he began to improve and at the end of the sixth month his coccidioidin reaction to 1:100 was +++. Another patient showed a + reaction to 1:100 coccidioidin on the fourth day of his illness, disseminated on the thirteenth day and on the eighteenth day still had only a + reaction. His serology was also negative. He was not retested until the seventy-fifth day of his illness when the biopsy of a nodule in his abdominal wall revealed *Coccidioides immitis*. By that time his elevated sedimentation rate was back to normal and he was feeling fine. His 1:100 coccidioidin test was +++ and his serum fixed complement. These 2 patients had no or only slight sensitivity prior to dissemination which became strong after recovery. Our other patient, No. 13 of Denenholz and Cheney (39), reacted +++ (100 mm.) to 1:100 coccidioidin, six days after his onset. He disseminated twenty days after his onset and twelve days later reacted only 9 mm. to the same dilution. Then on transfer to Hammond General Hospital he failed to react to 1:100 coccidioidin and on the fifty-second day of his illness was negative to 1:10 coccidioidin. Approximately six weeks later he began to improve and during the following two years he made a complete clinical recovery. His sedimentation rate is normal and his complement fixation titer has fallen to a low level. Two years and ten months after his onset he was retested. The 1:100 coccidioidin reaction was +++ (60 x 60 mm.) and the 1:1000 dilution measured 22 x 22 mm. However, we have had 2 other patients with disseminated infections who have *not* reestablished strong sensitivity after recovery. One patient had a +++ reaction to 1:100 dilution on the eighth day of illness. He disseminated on the twenty-seventh day and six weeks later had a + (8 mm.) reaction. He had only two skin lesions which eventually were excised and healed completely. After

the excision and a year after his dissemination, his reaction to 1:100 coccidioidin still measured only 9 mm. Another soldier developed coccidioidal peritonitis which was diagnosed only by demonstration of *Coccidioides* in the omental biopsy. He made a complete clinical recovery, his sedimentation rate returned to normal, his complement fixing titer fell to a low level and after a few months on limited service he was placed on full duty. His 1:100 coccidioidin test remained negative throughout his illness and was still negative two years after his onset and a year after his full duty status. Thus we see that establishment or reestablishment of coccidioidin sensitivity in patients with disseminated infection does not necessarily accompany clinical improvement. However, just as loss of coccidioidin sensitivity is an ominous prognostic sign, so the development of sensitivity is very encouraging.

#### CONTROLS AND SYRINGES

Asparagine synthetic medium was selected in order to eliminate the necessity of controls. Long experience with tuberculin has indicated that the delayed type of reaction does not result from the constituents of this medium. We did use controls at first but after over 500 tests with negative results, we stopped using control solution or distributing it. The first time we used the control material on ourselves, all of the laboratory group reacted slightly to the control and vigorously to the coccidioidin. We recognized that the reaction was probably the result of coccidioidin adsorbed on the wall of the syringe and when new syringes were used, the control injections evoked no response. Thereafter, we emphasized the necessity of using fresh syringes or soaking them in dichromate cleaning solution over night or boiling them in the solution. As we have seen, autoclaving does not inactivate coccidioidin, even the small amount adsorbed on syringes.

#### SENSITIZATION BY COCCIDIOIDIN

The nature of the active principle in coccidioidin is not yet understood. Hirsch, Benson and D'Andrea (4, 5) referred to it as a "Specific Soluble Substance" and indicated its polysaccharide as well as nitrogen content. Stewart and Kimura (12) indicate their belief that it is a polysaccharide. The polysaccharide component was studied by Hassid, Baker and McCready (30) who reported on its chemical composition. They indicated that the polysaccharide contained 3.2 per cent nitrogen (0.6 per cent as amino acid). They could demonstrate no positive specific protein test (Millon, xanthoproteic, glyoxylic acid or biuret tests). They suggest that the nitrogenous substance was probably some compound other than protein.

Dr. Florence Seibert, Dr. Joseph Aronson and Mr. H. J. Henderson of the Henry Phipps Institute in Philadelphia carried on analyses of coccidioidin until interrupted by the war. They used ultrafiltration concentration and separation by electrophoresis. Their studies, even of the polysaccharide analyzed by Hassid, Baker and McCready, indicated a combination of "protein" and polysaccharide. The skin tests and precipitin tests we made on the

components which Seibert separated by electrophoresis indicated that the allergic reactions followed the pattern of the "protein" concentration rather than the "carbohydrate" concentration. The situation is still not clear.

From the practical point of view, one very important consideration is whether coccidioidin will sensitize. Hirsch and D'Andrea (5b) indicated that they could sensitize animals with their coccidioidin as well as with killed mycelia. While we sensitized animals with killed mycelial suspensions, we were not able to sensitize guinea pigs using known potent coccidioidin. Undiluted coccidioidin was given 1.0 ml. intracutaneously in one series and 5.0 ml. intraperitoneally in another series at weekly intervals four times. Other guinea pigs were given 0.1 ml. undiluted coccidioidin daily for three weeks. A month after injections ceased the animals still did not react to 0.1 ml. undiluted coccidioidin.

Because guinea pigs do not develop the strong sensitivity seen in man, volunteer medical students were given 0.1 ml. undiluted coccidioidin intracutaneously in the volar surface of the left forearm. Deliberate attempt was made to retest the same place to evaluate the possibility of local tissue sensitivity. Five were tested twice at yearly intervals. One was tested five times at monthly intervals. Another was tested a year after the initial test, then three months later, three times more at four day intervals and the seventh time seven months later. Another student was given 8 intracutaneous injections at monthly intervals and a ninth five months later. In no instance was there development of sensitivity.

While not really as rigorous as the above tests, the Army experience with coccidioidin in 1:100 dilution gave hundreds of instances of five to ten retests without sensitization. C. O. C., who was a most diligent collaborator, took a coccidioidin test each time we visited Gardner Field. He was negative twelve times. His thirteenth test was positive, but it was given two days after the onset of a severe coccidioidal infection, thereby establishing his capability of reacting. Thus a *bona fide* change from a negative to positive coccidioidin status cannot be deemed the result of sensitization by the coccidioidin but signifies a coccidioidal infection. Clark and Gilmore (47) indicated a similar conclusion in their Army retesting experience.

Information gained by a coccidioidin test is very important in the interpretation of serological tests. Not only does the active principle of coccidioidin fail to sensitize, but also does it not evoke complement fixing or precipitin antibodies in those already sensitized. Scores of three and four plus coccidioidin reactions failed to evoke these humoral antibodies. Also repeatedly titrating as many as twenty lots of coccidioidin in 1:100, 1:1000 and 1:10,000 dilutions (figure 1) failed to result in positive coccidioidal serology. Therefore the coccidioidin test should not be withheld prior to obtaining a serum specimen. It serves as a very necessary "screen" to establish whether serological tests are indicated.

Even if there is a "protein" component in the coccidioidin, its fortunate lack of complicating antigenic characteristics could be explainable (53) by its low concentration (0.09 mgm. per cc.) together with possible haptene-like nature.

## DILUTION OF COCCIDIOIDIN

The optimal concentration for coccidioidin depends upon the purpose of use. During our erythema nodosum studies we used 1:1000 dilution. With the marked sensitivity shown by such patients, actually a 1:10,000 dilution usually will suffice. Several experienced investigators (39, 40, 44) have indicated the general applicability of 1:1000 coccidioidin for hospitalized active cases. For the undisseminated cases, if repeated, that dilution will pick up all the active infections. As we have seen, however, even 1:100 dilution is frequently negative early in the disease. In patients with coccidioidal pulmonary cavities of some duration, the 1:1000 frequently is insufficient and one should drop down to a 1:10 dilution before concluding it is negative. We have already seen that with disseminated infections even coccidioidin diluted 1:10 is frequently negative. Increasing concentration as needed to determine level of sensitivity is advisable in patients with coccidioidal granuloma. However, in 1:10 dilution the "non-specific" reactions of those from the middle west and south are greatly increased in frequency, so interpretation may be complicated.

In surveys it is advisable to use a 1:100 dilution as approximately 10 per cent may be missed with 1:1000 coccidioidin. During several trips to Minter Field, new arrivals were given both 1:100 and 1:1000 dilutions of coccidioidin in the volar aspects of the left forearm until a series of 200 reactors was accumulated. They were all residents of endemic areas over a period of years, care being taken to eliminate from the group any new arrivals. In that way we endeavored to sample older infections. The percentage of reactions in the 200 was as follows:

DEGREE OF REACTION	PERCENTAGE WITH	
	1:100	1:1000
++++	20.5	9.0
+++	27.0	31.0
++	30.0	23.5
+	22.5	25.5
0	0	11.0

Thus, while the severity of the reactions may be reduced considerably, an appreciable number of sensitive persons will be missed if coccidioidin weaker than 1:100 is used.

Of course, if there were any risk of activating a coccidioidal infection or of disseminating one, there would be reason to approach the test more circumspectly. While a ++++ reaction is quite uncomfortable, only twice in the scores of thousands of tests we performed was it necessary to relieve the person of duties. Both these men had very severe edema involving most of the forearm. Within two days they had recovered. Frequently with the severe local reaction there is also malaise and occasionally a degree or two of fever. However, never have we seen an old infection reactivated. At one of our neighboring hospitals 3

former San Joaquin Valley residents were tested with undiluted coccidioidin and although all reacted violently and one of the resident staff had to be hospitalized; there were no sequelae. On many occasions when different lots of coccidioidin were being compared, the patients would have two + + + + coccidioidin reactions. We have records of several patients who had solitary disseminations and within the month after the dissemination react with a + + + + response. Even though their infections must have been "unstable" or they would not have had the original dissemination, the coccidioidin did not shake out more. Furthermore, there is no focal reaction around a cutaneous disseminated lesion even in the few in that category who are highly sensitive. Roentgenograms taken before and after severe coccidioidin reactions during convalescence show no focal flare either. Thus, the worst that can ensue after a violent response to coccidioidin is a sore arm and temporary discomfort. Also, during active infection, occasionally a bout of erythema nodosum or erythema multiforme may be precipitated.

#### STABILITY OF COCCIDIOIDIN

The stability of coccidioidin, both diluted and undiluted, is of great practical importance. Through the years we have included some of our old lots of coccidioidin when testing new lots. By using the skin of the anterior femoral regions of both extremities, one can accommodate two dozen simultaneous tests. The only problem has been the gradually decreasing sensitivity previously alluded to. Using 0.3 ml. of 1:100 dilutions on March 31, 1947, confirmed April 2 by 0.1 ml. of 1:10 dilutions, we found that our first asparagine synthetic medium Lot 2 (harvested February 18, 1938, over nine years before) and Lot 3 (harvested June 13, 1938, nearly nine years before), appeared still fully potent and comparable to Lot 9 (harvested August 18, 1940) and Lot 29-31 completed March 25, 1945. Moreover, we compared Lot 3 which had been kept refrigerated with that which had been kept six years in the glove compartment of an automobile in the San Joaquin Valley and then nearly three years more at room temperature. The two reactions were identical. It would appear that undiluted coccidioidin remains fully potent for many years if not indefinitely.

The stability of diluted coccidioidin was also investigated. On the following dates, 0.2 ml. of undiluted Lot 9 coccidioidin were added to 19.8 ml. of sterile physiological saline solution without preservative in a rubber stoppered 30 ml. hard glass bottle and refrigerated: December 2, 1942, March 8, 1943, April 26, 1943, May 24, 1943 and September 24, 1943. Baker's Lot 9 "polysaccharide" (30) from a stock dilution of 1 mg. per ml. was also diluted 1:100 on the latter date. On September 24, 1943, two 6 ml. portions of these 1:100 dilutions were withdrawn from each bottle and placed in similar sterile rubber stoppered bottles. One set of bottles was kept at 3°C., one at room temperature and the third at 37°C. At first every month, then every three months and finally every six to eight months they were tested together with freshly diluted 1:100 Lot 9 and any new batches of coccidioidin undergoing preliminary determination of potency or old lots being rechecked. On March 31, 1947, four years and five months

after the initial dilution, the refrigerated 1:100 material still showed no reduction in potency compared with freshly diluted Lot 9. The same was true with the diluted material kept at room temperature for three and a half years. The incubated material remained fully potent for five and a half months (until March 12, 1944). Two months later (May 15, 1944) there was considerable reduction in potency and by ten and a half months there were only equivocal reactions.

These results indicate great stability even when coccidioidin is diluted. If the reacting chemical is a polysaccharide, it is quite stable and if a protein, is not only very weakly antigenic but also only slowly degraded.

#### CONTAMINATION OF COCCIDIOIDIN

However, it is imperative that the coccidioidin, whether diluted or not, be kept sterile. In the Station Hospitals sometimes we found that patients with undisseminated coccidioidal disease purportedly negative to coccidioidin had been tested with material which was contaminated. When tested with uncontaminated coccidioidin diluted even longer in the past, they reacted. Not only does contamination inactivate the coccidioidin but also at other times may it result in false positives. On several occasions the infirmaries would deluge the hospital wards with patients who later failed to react to coccidioidin. The infirmary stock coccidioidin always proved to be very turbid at that time.

#### ERRORS IN TECHNIQUE

Already we have seen three possible errors in coccidioidin testing: first, reading the test too soon or too late; second, using glassware on which other biologicals (like tuberculin) may have been adsorbed; third, contaminating the diluted coccidioidin. In addition there are the difficulties inherent in any intracutaneous test, injecting an insufficient amount or burying the coccidioidin subcutaneously. Another error has occurred when the coccidioidin, while evoking induration, produces only a faint pink which is not noticed. These faults frequently cause confusion. We have carried on extensive correspondence with some medical officers who kept reporting negative skin tests in patients with erythema nodosum and from whom we could get positive coccidioidal serological reactions. When these patients were transferred to the A.A.F. Regional Hospital at Santa Ana, the results of the skin tests would be positive. In other instances former long-time residents of an endemic area would be reported to have a negative coccidioidin and then a positive one. On the basis of this "change-over" they would be diagnosed as having recently acquired a coccidioidal infection after an incubation period of years. By the time patients worked their way back to the Fitzsimons General Hospital, the superb resumé sent by Fitzsimons to accompany serum specimens often would oscillate between +++ and negative coccidioidin reactions. Of course, there may be fluctuations of sensitivity, but they rarely swing so wildly back and forth. Thus, only if the test is carefully performed will coccidioidin hold its rightful place as the first step in the diagnosis of coccidioidal infection.

## SUMMARY

The preparation of coccidioidin is described. Various strains of *Coccidioides* are similar in their capacity to produce coccidioidin in asparagin synthetic medium. No difference is noted when the mat is ground in the medium or various filtering methods are used. The coccidioidin is very stable and no significant reduction in potency occurs even on heating at 250°C. for ten minutes. However, various lots frequently differ in potency and in specificity. Therefore, new lots of coccidioidin should be standardized on humans who include nonreactors, reactors and "equivocal" reactors.

The coccidioidin sensitivity is the usual "bacterial" type and is not transferrable passively. The length of time for the development of sensitivity is discussed together with the increase in sensitivity and relation of erythema nodosum. The sensitivity is quite durable and, although it may wane, the loss is usually slow. Limited experience does not bear out the theory that re-exposure to a coccidioidal environment has any significant effect on maintaining sensitivity.

A low level of coccidioidin sensitivity is generally associated with the dissemination of coccidioidal infection. The level of sensitivity has prognostic value. In several instances increasing sensitivity has been noted when the infection improves.

Technical aspects in coccidioidin testing are considered. The asparagin synthetic medium requires no control. However, other biologicals adsorbed on syringes or other glassware used in diluting may cause confusion. The coccidioidin is not significantly antigenic; therefore, development of sensitivity between tests is valid evidence of coccidioidal infection. Moreover, the tests do not stimulate the formation of humoral antibodies and should be performed prior to serological procedures for the additional information they furnish. The proper dilution of the coccidioidin is stressed. Severe reactions cause local discomfort and occasionally fever and malaise, but they do not activate a quiescent infection; they do not result in a dissemination of an infection and they do not produce an adverse effect on an acute initial illness other than occasionally bringing on erythema nodosum or erythema multiforme. Undiluted coccidioidin is stable for at least nine years and even diluted, if kept uncontaminated, is fully potent for many months. However, contamination of the diluted coccidioidin, injection subcutaneously rather than intracutaneously and inaccuracy of readings are all pitfalls which invalidate the test.

## SUMARIO

*El Empleo de la Coccidioidina*

Describe la preparación de coccidioidina. Varias cepas de *Coccidioides* se muestran semejantes en su capacidad para producir coccidioidina en un medio sintético de asparagina, sin que se note diferencia cuando se tritura el material en el medio o se emplean varias técnicas de filtración. La coccidioidina es muy estable y no sobreviene mayor pérdida de potencia ni aun con la calcfacción a

250°C. por 10 minutos, aunque varios lotes discrepan frecuentemente en potencia y especificidad. Por consiguiente, los nuevos lotes de coccidioidina deben ser estandarizados en seres humanos que comprendan reactores, negativos y reactores "dudosos."

La sensibilidad a la coccidioidina es del habitual tipo "bacteriano" y no se transmite pasivamente. Discútese el tiempo que tarda en presentarse la sensibilidad con su exaltación y relación con el eritema nudoso. Es bastante duradera y aunque puede atenuarse, la pérdida suele ser lenta. Una experiencia limitada no apoya la teoría de que la reexposición a un ambiente coccidioidico ejerza mayor efecto sobre el mantenimiento de la sensibilidad.

Un bajo tenor de sensibilidad a la coccidioidina se asocia generalmente con la difusión de la coccidioidosis. El índice de sensibilidad posee valor pronóstico. En varios casos se ha notado aumento de la sensibilidad al ir mejorando la infección.

Al considerar las fases técnicas de la comprobación con coccidioidina, señálase que el medio sintético de asparagina no exige fiscalización, si bien otros productos biológicos adsorbidos en las jeringas u otra cristalería pueden ocasionar confusión. La coccidioidina no es significativamente antigénica, por lo cual la aparición de sensibilidad entre reacciones constituye prueba válida de la existencia de coccidioidosis. Las pruebas tampoco excitan la formación de anticuerpos humorales y deben ser realizadas con anterioridad a los procedimientos serológicos por la información suplementaria que aportan. Recálcase la dilución apropiada de la coccidioidina, pues las reacciones intensas ocasionan incomodidad local y a veces fiebre y malestar, pero no activan una infección quiescente. Tampoco dan por resultado difusión de la infección ni producen efecto adverso sobre una enfermedad inicial aguda aparte de provocar de cuando en cuando un eritema nudoso o multiforme. La coccidioidina sin diluir permanece estable por los menos nueve años, y aun diluída, si se mantiene sin contaminar, retiene su plena potencia por muchos meses. Sin embargo, la contaminación de la coccidioidina diluída, la inyección subcutánea en vez de intracutánea y la inexactitud en las lecturas constituyen asechanzas que inutilizan la prueba.

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# HISTOPLASMOSIS AND PULMONARY CALCIFICATIONS<sup>1,2</sup>

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It is only two years since the relationship of histoplasmin sensitivity to pulmonary calcification was first shown. In that time, the great interest aroused has resulted in the publication of a considerable number of papers on the subject. Also, considerable effort has been expended in attempts to demonstrate a benign type of infection with *Histoplasma capsulatum*. In this paper we will attempt to review what we think is significant of this material and to present our concepts of the infection as it appears to occur.

## HISTOPLASMIN SENSITIVITY AND PULMONARY CALCIFICATION

*General Considerations:* Preliminary studies by members of the Department of Pediatrics at Vanderbilt University (1) with histoplasmin tests in 1945 showed that histoplasmin sensitivity was not uncommon and that such sensitivity was sometimes associated with pulmonary calcifications not attributable to tuberculosis. Palmer (2) studying nurse cadets was able to show a high degree of correlation between pulmonary calcification and histoplasmin sensitivity: while only 24.9 per cent of the group as a whole reacted to histoplasmin, 84.7 per cent of those with pulmonary calcifications reacted to this antigen; 10.2 per cent of the group as a whole reacted to tuberculin, and 21.4 per cent of those with calcifications reacted to tuberculin. Our studies (1, 3, 4) have shown similarly that 87.4 per cent of Tennessee residents with calcification react to histoplasmin, while only 18.8 per cent react to tuberculin. This is almost the exact prevalence of tuberculin sensitivity for the whole of our group.

On the other hand, Olsen, Bell and Emmons (5) in a study of the residents of Loudoun County, Virginia, were unable to find a positive association between a reaction to histoplasmin or tuberculin and the presence of pulmonary calcification, though there was a correlation between residents in a household giving a history of tuberculosis and the presence of pulmonary calcification. (Curiously, residence in a household with a history of tuberculosis did not enhance the probability of reacting to tuberculin, though it did increase the probability of the individual reacting to histoplasmin).

Waring and Gregg, using our histoplasmin, made a study of children in Charleston, South Carolina. They found only 8 of 349 children with pulmonary calcification who did not react to tuberculin. Of the 8, 5 reacted to histoplasmin, though the prevalence of histoplasmin reactions in that area is only 2 in 121 tests, or 1.6 per cent. It is of further interest that the 5 histoplasmin reactors among the 8 with pulmonary calcification who failed to react to tuberculin were

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either natives of areas of high incidence of histoplasmin sensitivity or had made extended visits to such areas.

McWeeney, Crowe, and Dunleavy (7) in a study of 320 Irish children found no calcifications in 191 tuberculin negative children, nor did they find, in the 320 children studied, a single reactor to the histoplasmin which we supplied.

Alman and Opinsky (8) found 16 reactors to histoplasmin in 441 children from the District of Columbia area. Of these reactors 13 or 81.2 had pulmonary calcifications. These authors do not, unfortunately, give the prevalence of such lesions in the group as a whole.

These studies in general show that pulmonary calcifications are statistically related to histoplasmin sensitivity, and that pulmonary calcifications are much more prevalent in communities where histoplasmin sensitivity is highly prevalent than in areas with low prevalence of histoplasmin sensitivity.

*Geographical variations:* Geographical variations in the prevalence of pulmonary calcifications has been shown by a number of investigators, most strikingly by Long and Stearns (9). They showed that Army inductees from the Western Appalachian slope and the bordering states west of the Mississippi and north of the Ohio showed a greater prevalence of pulmonary calcifications than those from other areas. The studies of Palmer (2, 10) and our studies (4) have shown that histoplasmin sensitivity is much more prevalent in this area of excessive pulmonary calcifications. The contrasting study of Waring and Gregg (6) seems of great significance in this respect. They found pulmonary calcifications in only 3.4 per cent of their school children in an area where the index of histoplasmin sensitivity was low, as contrasted with over 40 per cent in the group reported by Olsen, Bell and Emmons (5), 55.1 per cent in our study groups, and 12.7 per cent in groups studied by Furculow, High and Allen—all groups from areas of high prevalence of histoplasmin sensitivity. In the West in areas of endemic coccidioidomycosis, Cox and Smith and Aronson, Saylor and Parr (12) have shown that pulmonary calcifications are associated with coccidioidomycosis.

We believe that these studies clearly indicate an intimate relationship between pulmonary calcification and histoplasmin sensitivity in the areas where such sensitivity is highly prevalent.

Histoplasmin sensitivity prevalence has been shown in the foregoing to vary greatly with geographical areas. We can also add (12) that in addition to the absence of reactors in Ireland, that none of several hundred individuals living in Holland reacted to histoplasmin, that there were no clear-cut positive reactions in more than a hundred persons tested in Curacao, that positive tests are encountered very infrequently in children in New York City, Buffalo and Rochester, New York, in Detroit, in New Orleans and in San Francisco. It has also been observed in Tennessee (14) that sensitivity to histoplasmin is more prevalent in areas adjacent to streams and other areas of dampness than it is on high dry ridges.

From these studies it is apparent that the question of histoplasmin sensitivity

and its relationship to pulmonary calcifications is one which may be of great importance in one locality and of no importance in another; and also that some factors of climate and physical geography must be of great significance in the epidemiology of histoplasmin sensitivity.

#### AGE RELATIONSHIPS IN HISTOPLASMIN SENSITIVITY

All observers with suitable study materials (1, 3, 5, 8, 10) have found an increasing percentage of reactors in childhood with increasing years. The rate of increase varies with the locality of the study but in all studies acquisition of histoplasmin sensitivity has occurred more rapidly in early life than did tuberculin sensitivity and was in such relationship to the development of pulmonary calcifications as to be interpretable as a relationship of cause and effect; a relationship which cannot be demonstrated for tuberculin sensitivity and pulmonary calcification in areas of high prevalence of pulmonary calcifications (3, 10). This seems particularly significant if one accepts the study of Hardy (15) showing that, for practicable purposes, persons with roentgenographically demonstrable tuberculosis do not lose their sensitivity to tuberculin over an average period of 14.6 years. It must be concluded, therefore, that in those children and young adults who have pulmonary calcifications but negative reactions to tuberculin some cause other than tuberculosis must account for their calcified lesions.

#### ROENTGENOGRAPHIC FINDINGS IN PERSONS WITH HISTOPLASMIN SENSITIVITY

The study of Long and Stearns (9) indicated that calcifications in the area of high prevalence were qualitatively different, that they were often massive, multiple and that there were excessive instances of "miliary calcifications." Our studies (1, 3) and independently those of Zwerling and Palmer (16) have shown that massive hilar lesions, the multiple peripheral lesions and the "miliary" calcifications are found much more commonly in association with histoplasmin sensitivity than with tuberculin sensitivity.

#### THE SIGNIFICANCE AND SPECIFICITY OF HISTOPLASMIN REACTIONS

The development of the histoplasmin test has in some instances led to the assumption that if a patient reacts he must have the disease. As a matter of fact, the converse is true of the fulminating infection where the majority of patients (4, (17-21)) have not reacted to known potent antigens. This fact must be accepted as indicating a form of anergy resulting from an overwhelming infection, the counterpart of which is well known in tuberculosis. The test cannot, therefore, be used in all illnesses to exclude the possibility of histoplasmosis.

The fact that at age 5 years, 50 per cent of our patients react to histoplasmin with an almost complete lack of history of any illness which we could then, or now, recognize as the primary infection, strictly limits the value of the test in diagnosing active disease processes. We will return to this point in the discus-

sion of our concept of the primary infection. Clinically histoplasmin can be used in much the same manner that tuberculin is used as an adjunct in excluding possible minor infections after the preallergic phase, and as an exclusion test in patients who do not have fulminating infections.

The study of Emmons (22) showed that there was a marked degree of cross-reactions with histoplasmin in heterologous fungus infections. He has accordingly cast doubt on the question of histoplasmosis being responsible for the pulmonary calcifications observed; also he and his associates (5) were unable in the survey of Loudoun County, Virginia, to find any evidence for the existence of a mild form of histoplasmosis. Howell (23) in a recent study has shown that different lots of histoplasmin vary markedly in their critical titers, an experience which we have shared (21). He also showed that good antigens used at their critical titers yielded very few cross-reactions with heterologous fungus infections. These studies serve to emphasize the need for improving and standardizing histoplasmin preparations.<sup>3</sup>

#### THE INFECTION-HISTOPLASMOSIS

The literature has been filled with case reports of clinically recognizable histoplasmosis, starting with the cases of Darling (24) in 1906 and culminating with the reviews of Meleney (25) and Parsons and Zarafonitis (17); now new cases are being recognized continuously. Certainly increasing knowledge of the disease has resulted in increasing diagnoses to the point where it is no longer an extremely rare disease. While less than a hundred cases have been reported, it is safe to say that more are being recognized than are reported. The clinical manifestations of the severe infections are protean. These may be epitomized by saying that there is irregular low grade fever, hepatomegaly and splenomegaly with anemia and leucopenia. There may be general glandular enlargement and frequently there are symptoms of pulmonary infection; pleural pain, cough and expectoration. Many patients have had symptoms referable to ulcerative lesions of the gastrointestinal tract, including the mouth and oropharynx. The duration of the disease in these patients is from a few weeks to as long as fifteen to twenty years and in the great majority the infection has been considered ultimately fatal. The diagnosis in these cases can usually be established by adequate cultural techniques and the examination of biopsy material, lymph nodes and sternal marrow.

It is perhaps significant that 15 cases of proven histoplasmosis have been recognized at Vanderbilt Hospital and that tissues from a half dozen other cases, culled from a group of nonspecific granulomatous lesions and from tuberculin negative cases with morphological diagnoses of hilar tuberculosis, are highly suspicious.

While these cases are of great academic interest they are from our viewpoint much less important than those patients who have minimal, nonfatal, almost nonsymptomatic infections.

Since the relationship of pulmonary calcifications to histoplasmin sensitivity

<sup>3</sup> We are pleased to report that the Research Committee of your Society is giving us financial aid and encouragement in this phase of our study.

was first pointed out, we, and others, have been engaged in a search for minimal infections. In this problem one is faced with the same difficulty that would be encountered after sixty-five years of extensive investigations in attempting to prove bacteriologically the existence of minimal primary tuberculosis. In fact, we have found that an additional number of technical difficulties arise which make the solution of the problem a tedious labor.

In tissues *H. capsulatum* yeast cells are found almost entirely intracellularly and may multiply chiefly if not exclusively within the cells. Thus, unless the lesion goes on to caseation and ulceration one cannot expect the release of organisms; also, the sputum or gastric washings would be negative. This expectation has been confirmed in several ways. We have been unable to demonstrate or cultivate the organisms from the sputum in one case with a fatal military infection and have failed in other instances of what seemed to be almost certain infections to show organisms in the sputum or gastric washings or both.

Early attempts to cultivate the organisms from autopsy materials *in vitro* and by passage through experimental animals were unsuccessful. The first because of the invariable contaminants; the second because the organism was often either of such low virulence that it was incapable of producing a significant lesion or it was no longer viable. Recently Womack, of the Department of Pathology at Vanderbilt University School of Medicine (27) has succeeded in cultivating the organisms from the lung and lymph node lesions of minimal cases. While this work is still in a preliminary phase, it gives excellent promise of establishing satisfactory biological proof of the existence of minimal infections. Certainly the repetition of these findings is reaching a proportion where they could not all be early fulminating cases.<sup>4</sup>

Another approach to the solution of the problem of the minimal infection has been the study of pulmonary roentgenograms in children who have recently developed histoplasmin sensitivity. Infants being followed in well-baby clinics are given repeated histoplasmin tests and as sensitivity develops roentgenograms are made. In a number of these infants we have been able to show pulmonary lesions which were not giving rise to significant symptoms. One of the difficulties of this approach has been our inability to secure technically good roentgenograms. These infants have been followed insufficiently long to determine whether or not these lesions go on to calcification. In 2 instances we have observed hilar lymphadenopathy of a degree sufficient to produce atelectasis and cough in young children who were repeatedly tuberculin-negative and who had strongly positive histoplasmin tests.

We believe that these cases represent minimal infections with a fungus capable of producing histoplasmin sensitivity and which is presumably histoplasmosis in a benign form.

#### SUMMARY

The apparently significant features of the relation of histoplasmin sensitivity to pulmonary calcifications have been briefly reviewed.

<sup>4</sup> This material will be reported in detail elsewhere.



The available, preliminary evidence for the existence of benign forms of histoplasmosis has been stated.

# SUMARIO

## *Histoplasmosis y Calcificaciones Pulmonares*

Repásanse sucintamente los puntos aparentemente significativos de la relación de la sensibilidad a la histoplasmina con las calcificaciones pulmonares.

Expónense los datos preliminares disponibles con respecto a la existencia de formas benignas de la histoplasmosis.

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## DISCUSSION<sup>1</sup>

### Symposium on Nontuberculous Pulmonary Diseases

DAVID T. SMITH<sup>2</sup>

Two points of diagnostic significance and one of therapy should be mentioned in connection with Doctor Eaton's paper. The clinical and X-ray pictures of virus pneumonia may at times be duplicated by early acute tuberculosis, and patients diagnosed as having virus infections should not be dismissed until the chest films are entirely clear. A series of patients with pulmonary tularemia, without peripheral lesions, have been reported recently from the Vanderbilt Clinic. In the early stages of the disease the clinical and X-ray findings were practically identical with those of virus pneumonia. We are now studying in North Carolina a small epidemic of ornithosis (psittacosis) contracted from pigeons. The more severely ill patients were all treated with large doses of penicillin (1:3,000,000 units) and all the patients have recovered.

Doctor Kay has certainly demonstrated the frequent occurrence of actinomycetes in the mouth and in the sputum and lungs of patients with suppurative pulmonary disease. In a particular case these actinomycetes may be (1) primary, (2) secondary or (3) saprophytic. In our experience with primary actinomycosis of the lungs, with or without sinuses in the chest wall, the sputum is never fetid, large single or multiple cavities do not occur, multiple small suppurative areas are characteristic and are accompanied by massive fibrosis. Hemoptysis occurs but not as frequently as in infected neoplasms and in the fuso-spirochetal type of infections. Infections, where the fuso-spirochetal type of organism predominates and actinomycetes is absent, usually have fetid sputum, frequently have large cavities, and hemoptysis is very common. In many of Doctor Kay's patients both types of infection were present. The presence of primary bronchial actinomycosis seems fairly well established, but I would regard actinomycetes first in the cases of bronchiectasis as saprophytic until further proof of their relation to the disease is obtained.

Doctor Smith mentioned his failure to induce sensitivity to coccidioidin by the injection of coccidioidin. I would like to ask if he has tried to produce sensitivity in animals or man with heat-killed vaccines from cultures of *Coccidioides immitis*?

Doctor Peterson mentioned the low incidence of histoplasmin sensitivity in Georgia and the Carolinas. We have confirmed this finding in our students. There is, however, a high incidence of clinical blastomycosis in this area and we are beginning to find instances of sensitivity to blastomycetin in healthy individuals who are negative to both coccidioidin and histoplasmin.

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# FATAL COCCIDIOIDOMYCOSIS<sup>1</sup>

## A Case of a Laboratory Infection

DAVID T. SMITH AND EVERETT RICHARD HARRELL, JR.

Subclinical and clinical infections with *Coccidioides immitis*, have occurred in most laboratories in which the organism has been studied (8). Only two cases of laboratory infections have been published. The first was a Stanford medical student who developed a severe primary coccidioidomycosis but recovered and remained well for at least eleven years (2). The second case occurred in a fellow in the Department of Bacteriology at the University of Nebraska. He developed a primary pulmonary infection followed by metastatic lesions on the plantar surface of the left foot. All symptoms disappeared after three months, but after four years chills and fever recurred and *Coccidioides immitis* was found in a subcutaneous nodule in the left leg. After treatment with antimony and potassium tartrate, the lesion healed and the symptoms subsided in four weeks. This patient has remained well for at least fifteen years (5-7).

There was a small laboratory epidemic in our hospital about eighteen months ago which followed the accidental contamination of the outside of some flasks with liquid cultures of *Coccidioides immitis*. Presumably, some of the infectious arthrospores dried on the flask and contaminated the air. Several workers in the cleaning room came into direct contact with the flasks before they were autoclaved.

Four laboratory workers who were in the room with the flasks later showed positive skin tests to a 1:1000 dilution of a standard coccidioidin supplied to us by Dr. Charles E. Smith. Five laboratory workers who were on the same floor but several doors away had negative skin tests to 1:100 dilution of coccidioidin. Of the 5 Negro workers in the cleaning room, 2 had negative skin tests to a 1:100 dilution of coccidioidin; one had a mild reaction; one a severe reaction, and one developed a primary pulmonary coccidioidomycosis which progressed to a generalized disease with death from meningitis. This case is being reported in detail.

## CASE REPORT

A 74-year-old colored male hospital employee reported to the Medical Out-patient Department July 29, 1946 with a story of an acute upper respiratory infection of four days' duration. Twenty-four hours before coming to the clinic he developed inspiratory pulmonary pain, a sharp chill, and began to cough up yellow mucopurulent sputum. Rales were heard at the left base posteriorly. A chest film (figure 1) was made which showed areas of soft infiltration in the second and fourth interspaces on the right and a more extensive area at the left base above the diaphragm. The left diaphragm was flattened and the left costophrenic angle obliterated.

Sulfadiazine and a codeine cough mixture were prescribed, and the patient was sent home under the care of his family physician. For the next ten days his symptoms and

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signs increased progressively until he was admitted to the Duke Hospital August 8, 1946 with the diagnosis of bronchial pneumonia.

The patient was a dishwasher in the Bacteriology Laboratory where he was exposed to Petri dishes and test tubes in which various types of bacteria and fungi had been grown. He collected this glassware from the laboratory and delivered it to the sterilizing room for autoclaving. Careful questioning revealed that he had never traveled out of the State of North Carolina.

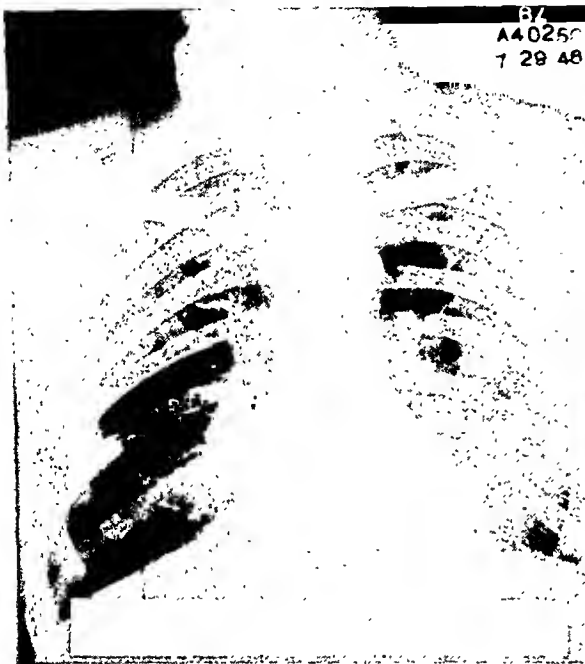


FIG. 1

FIG. 1. (Left.) Chest film of 7/29/46 showing infiltration in the outer third of the right upper lobe and at the left base. The costophrenic angle at the left base is obliterated.

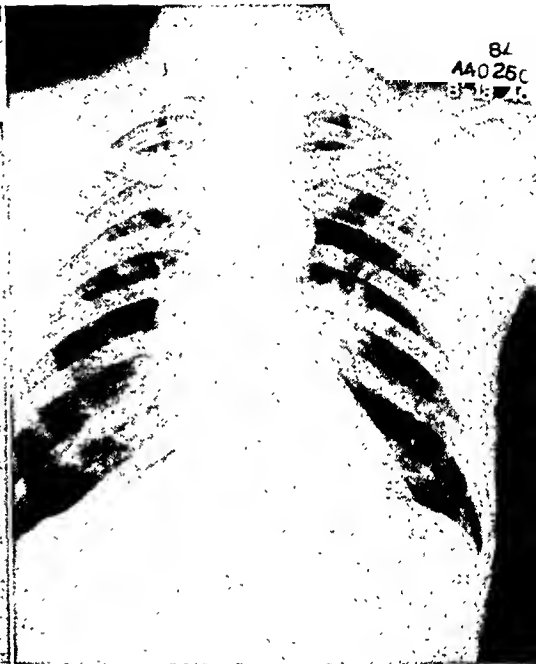


FIG. 2

FIG. 2. (Right.) Chest film of 8/13/46 showing clearing of the process in the right upper lobe and complete disappearance of the lesion at the left base. Note the progressive enlargement of the hilar lymph nodes.

On admission, the patient was found to be moderately ill with a temperature of 102°F., pulse 100, respiration 28, and a blood pressure of 147/90. Physical examination showed diminished breath sounds and dullness at both bases with a few crackling râles scattered over the entire chest. A portable X-ray film showed a diffuse clouding of both bases with obliteration of the left diaphragmatic angle. There were soft, diffuse shadows in the second and fourth interspaces on the right side.

Laboratory examination showed the hemoglobin to be 12.6 g. (82 per cent), red cells 4,350,000; white cells 18,000 with 85 per cent polymorpho-nuclear cells, 6 eosinophiles, no basophiles, 2 monocytes, 2 large lymphocytes and 5 small lymphocytes. Sedimentation rate was 42 mm. per hour. Kline, Kalm and Mazzini tests were negative. Intracutaneous tuberculin test to 1:1000 OT was positive. Repeated examinations of the sputum failed to reveal acid-fast organisms; both direct examinations and cultures showed no fungi.

The sputum was mucopurulent and yellow and routine cultures of the sputum grew non-hemolytic *Staphylococcus aureus*, alpha hemolytic streptococci, *N. sicca* and *N. catarrhalis*.

A diagnosis of staphylococcic bronchial pneumonia was made and the patient was started on 40,000 units of penicillin every four hours. Penicillin was continued for twenty

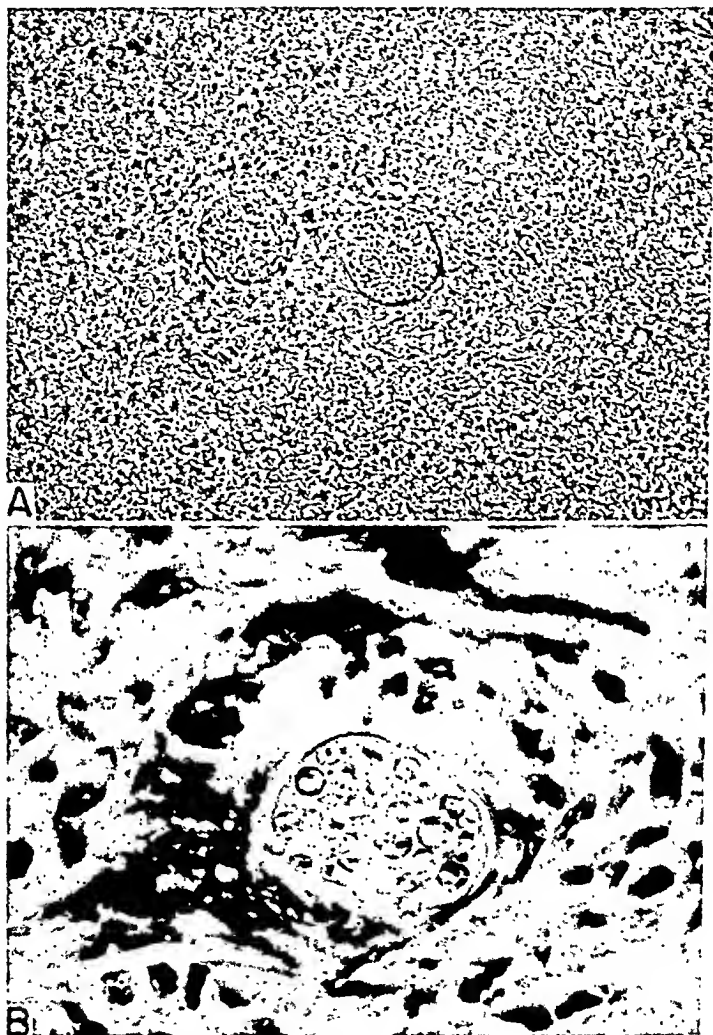


FIG. 3. (a) Endosporulating spherules seen in preparation of pus from sputum (235 X).

(b) Section of lymph node biopsy showing large, thick-walled spherule with endospores in a giant cell (485 X).

days. The râles in his chest decreased and he improved somewhat in general but continued to have a spiking temperature which ranged from 99 to 100°F. A new X-ray film made 8/13/46 showed the diaphragms to be clear, and there was considerable clearing of the pulmonary lesions, but there was now a marked increase in the lymph nodes in the hilum of the lungs (figure 2). Skin tests to blastomycin, coccidioidin, histoplasmin and trichinellin antigens were all negative. The coccidioidin was repeated using a 1:100 dilution and a very slight reaction was obtained after twenty-four to forty-eight hours.

On August 30th a slight, general glandular enlargement was noted. A lymph node was removed from the right supraclavicular region for biopsy. A diagnosis of coccidioidomycosis was made from the lymph node (figure 3b). By this time, the yellow mucopurulent sputum had disappeared leaving only a few cubic centimeters of white mucoid material each day. Direct examination of this mucoid material revealed large numbers of typical spherules with endospores characteristic of *Coccidioides immitis* (figure 3a). The organisms were cultivated on a one per cent dextrose agar and isolated in pure culture without difficulty (figure 4). Complement fixation for coccidioidomycosis, using an antigen supplied to us by Dr. Charles E. Smith of Leland Stanford, Jr. University, showed complete fixation in a 1:4 dilution and partial fixation in a 1:32 dilution. The skin test to coccidioidin was never definitely positive.

On September 8, 1946 the patient had a severe chill and a few days later several subcutaneous nodules were found in the left thigh. Two nodules were removed, the characteristic organisms were not found in the sections but *C. immitis* was grown in pure culture from the other lymph node. The biopsy wound healed readily and the remaining nodules disappeared spontaneously during the next two weeks.

The temperature declined somewhat but continued to vary from 99 to 102°F. during October, November and December. About the 20th of November, the patient developed marked stiffness of the spine and generalized hyperalgesia of the skin. X-ray films of the spine showed no involvement of the vertebrae. After one week the hyperalgesia disappeared and the stiffness of the spine disappeared but he developed a dull, constant headache with very slight stiffness of the neck. He gradually became comatose and died January 11, 1947, 170 days after the onset of his first symptoms. The final diagnosis was progressive generalized coccidioidomycosis with terminal meningitis. Permission for a necropsy could not be obtained.

**Biopsy report:** The lymph node removed from the supraclavicular region was studied in the Department of Pathology. This lymph node showed all of the characteristic reactions to *Coccidioides immitis* which have been described in detail by Forbush (3). These fall into three basic patterns: The first is an acute, suppurative, inflammatory reaction; the second is a characteristic tuberculoid type of granulomatous, inflammatory reaction; and the third is a mixture of the first and second. In the suppurative type of reaction, organisms of certain specific types are found associated with the lesion. These are mature, sporulating forms of *Coccidioides immitis* which either have already ruptured, spilling the spores into the surrounding tissues or they are mature, sporulating forms on the verge of rupture, this being indicated by degenerative changes within the capsule of the parent organism. Inflammatory, cellular response to the spores and the sporulating organisms is characteristically and exclusively polymorphonuclear leukocytic. No giant cells and no mononuclear cells appear in the immediate environment of the organism.

In the second type of lesion, that is, the tuberculoid, granulomatous form, the cellular reaction consists chiefly of mononuclear phagocytes, multinucleated giant cells and a scattering of polymorphonuclear leukocytes. These elements combine to form characteristic tubercles. Within the giant cell and often within the tissue spaces, the spherule forms of *Coccidioides immitis*, not yet showing evidence of sporulation, are numerous.

In the third type of reaction, that is, the mixed type of reaction (a combination of suppuration and genuine granuloma) characteristic tubercle formation with its typical giant cells containing spherules constitutes the most characteristic histological feature. But even within the most typical epithelioid reactions, there are clusters of polymorphonuclear leukocytes. Similar cells are scattered rather diffusely throughout the field. The organisms in this mixed type of reaction appear in a great variety of developmental forms.

Thus, in the tissues from this biopsy, there are all the histological features essential to



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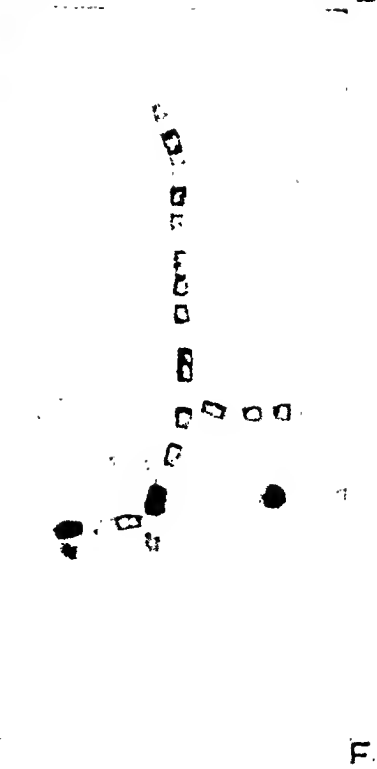
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C



E



F

the diagnosis of the disease and to the understanding of the fundamental pathological reactions that this interesting organism provokes.

#### DISCUSSION

Negroes, Mexicans and Filipinos are much more susceptible to progressive coccidioidomycosis than members of the Caucasian race. Various authors (1, 4) have estimated the ratio of increased susceptibility as ten or even twenty to one. Members of the susceptible races should not be employed as cleaners or janitors in laboratories where *Coccidioides immitis* is being studied unless they already have had a clinical or subclinical infection as shown by a positive skin test to coccidioidin.

When proper precautions are taken there is no danger in students' studying *Coccidioides immitis* in courses in Bacteriology and Mycology. This organism has been used in our classes for the past sixteen years without the development of a single case of clinical coccidioidomycosis. This past year a class of 50 was skin tested with coccidioidin three months after their last hypothetical exposure in the laboratory. There was only one positive test and this was in a student who had lived in western Texas for a number of years where the disease is known to occur. The cultures were given to the students in test tubes, not Petri dishes, as soon as definite arthrospores have developed and the students are instructed to wet the bacteriologic loops with a drop of sterile water before picking up the powdery aerial hyphae for transfer to a wet mount preparation on a slide. One of our technicians worked intermittently every two or three weeks with cultures of *Coccidioides immitis* over a period of two years. She still has a negative skin test with coccidioidin two years later.

#### SUMMARY AND CONCLUSION

The arthrospores of the cultural form of *Coccidioides immitis* are highly infectious. A number of laboratory epidemics have occurred, generally resulting in subclinical, but occasionally clinical, infections. A small epidemic in our laboratory resulted in 5 subclinical infections and one progressive, fatal case of coccidioidomycosis. This fatal case is reported in detail.

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FIG. 4. (a) *Coccidioides immitis* on Sabouraud's glucose agar. Six days at room temperature. Central aerial mycelium with wide border of moist mycelium on surface of agar.

(b) Photomicrograph of mycelium from six-day culture. Continuous septate hyphae with some evidence of anthrospore formation. Too early to make an identification (580 X).

(c) *Coccidioides immitis* on Sabouraud's glucose agar, ten days at room temperature. Loose, cottony aerial mycelium beginning to cover agar surface.

(d) Photomicrograph of mycelium from ten-day culture. Typical anthrospore formation allows identification (580 X).

(e) *Coccidioides immitis* on Sabouraud's glucose agar, fourteen days at room temperature. Profuse growth of aerial mycelium.

(f) Photomicrograph of growth in fourteen-day culture. The hyphae have broken up into anthrospores which makes the culture very dry and powdery. During this period of growth (old cultures) great precautions should be taken when transferring such powdery material (580 X).



The organism can be studied without danger of infection by classes in bacteriology and mycology if the cultures are dispensed in test tubes, not Petri dishes, and care is taken in opening the tubes and in keeping the powdery hyphae wet while transferring and studying the material.

#### SUMARIO Y CONCLUSIONES

##### *Coccidioidomycosis Letal: Infección de Laboratorio*

Los artrosporos del *Coccidioides immitis*, en cultivos, son sumamente infecciosos, y se han observados varias epidemias de laboratorio, culminando en infecciones por lo general subclínicas, pero de cuando en cuando, clínicas. En el laboratorio de los AA., un brote dió por resultado 5 infecciones subclínicas y un caso evolutivo letal de coccidioidomycosis, el cual se describe con todos sus detalles.

El microbio puede ser estudiado sin peligro de infección por las clases de bacteriología y micología si se dispersan los cultivos en tubos de ensayo, no placas de Petri, y se muestra cuidado al abrir los tubos y se mantienen humedecidas las polvorientas hifas mientras se hacen pases y estudia el material.

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## CASE-FINDING IN IOWA<sup>1</sup>

### Report on State-wide Clinics and Mass X-ray Surveys

L. H. FLANCHER<sup>2</sup>

The State of Iowa is one of the first states in the Union where an official agency, the State Department of Health, and a voluntary agency, the Iowa Tuberculosis Association, jointly sponsor and finance a program for the control and eradication of tuberculosis. This plan has been in operation since 1937.

Our state is mostly rural, only one city having more than 100,000 population, while ten have more than 25,000. There are nearly a thousand smaller cities, towns, and many cross-road villages. Farming is the backbone of the state's economy. The population of Iowa is about 2,500,000 persons.

In all our programs the county medical society must first give approval before we go into the county. The individual physician is also asked for his consent to visit any of his patients. X-ray diagnoses are sent to the family physician only, never to the patient direct.

The case-finding programs are state wide, on a county basis, and are divided as follows:

1. Examination of contacts of all known cases of tuberculosis, suspects, contacts of living patients, and of those reported by death certificates. All are tuberculin-tested by the family physician. Reactors are X-rayed at county conferences once each year. This is our basic program.

2. 35 mm. X-rays are taken of all teachers, school employees, and high school students in a county, rural and otherwise; all abnormal shadows found are followed up by large 14 x 17 X-rays.

3. 35 mm. X-rays of groups employed in industry are made, with 14 x 17 X-rays on all abnormal shadows. This particular program is carried on with the cooperation of the Industrial Hygiene Division of the State Department of Health. I wish to emphasize the fact that the various divisions in our health department cooperate very closely in all our programs.

4. 35 mm. X-rays will be taken of every man and woman in each county of the state. This program will be put into operation the latter part of 1947.

While not a routine program, we have just finished a survey of our 16 state institutions. We believe we are one of the first states to complete such a program.

Why does an organization or department interested chiefly in the control and eradication of tuberculosis, concern itself with a heart program which at first glance is entirely unrelated to the work at hand?

A careful study of mortality statistics in Iowa for the year 1944 shows that approximately one-third of all deaths were caused by heart diseases; in fact,

<sup>1</sup> Presented at the Conference on Heart Disease Programs at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 16, 1947.

<sup>2</sup> Director, Division of Tuberculosis Control, Iowa State Department of Health, Des Moines, Iowa.

8,154 deaths were caused by heart diseases out of a total of 26,165 deaths in the state. Moreover, heart diseases are the leading cause of death in nearly all age groups. This statement is also true of the United States as a whole.

Heart diseases are not a public health menace in the usual accepted meaning of the term. Webster says . . . "Menace . . . a threat, or to threaten." Therefore, in our opinion any disease which threatens our population to the extent that one-third of all deaths are caused by it is indeed a public health menace or a public health problem.

How can such a heart program function in conjunction with mass tuberculosis case-finding projects?

Suspicious heart conditions found in our tuberculosis case-finding programs have been reported routinely since 1943. Up until 1945 all suspect hearts were re-X-rayed on the basis of findings in our miniature film projects. Since then, in all our 35 mm. surveys the family physician has received a report on suspected heart conditions.

We use a double card in all miniature programs. When a heart condition is suspected, a special mimeographed slip is inclosed which reads as follows:

"Your miniature film shows shadows which are not entirely normal. We suggest you see your family physician for a thorough chest examination. He has been informed regarding the probable nature of the condition. A large X-ray film is not necessary."

All cards are returned to patients in sealed window envelopes. You will note that no mention is made of heart disease on this report.

In order to test the efficacy of such a program, questionnaires were sent to physicians covering the period from January 1, 1947 to May 1, 1947, when the 35 mm. high school program was completed. Four questions were asked: Did the patient report? Was a diagnosis of a heart condition made? If so, had you previously known of this condition? Is this service of value to you?

Questionnaires were sent to 134 physicians concerning 213 out of 341 suspicious heart conditions found among high school students. At this time (June, 1947) 87 replies or 65 per cent of the questionnaires sent out have been received. The number of students who reported to their physicians for examination was 92 or 43 per cent of the total; 47 students or 22 per cent of the 213 studied, failed to report; thus 74 students or 35 per cent of the group remained unaccounted for.

Of the 92 students who reported for examination, more than half (55 per cent) showed evidence of heart disease on physical examination and 45 per cent had no evidence of heart disease.

In answer to the question . . . "Had you previously known of this condition?" (in cases where a diagnosis of heart disease was made), the replies of the physicians were evenly divided as to "known" and "not known". All physicians who replied to the questionnaire stated that the service was of value to them, regardless of the presence or absence of a heart condition.

These questionnaires covered the high school program, numbering 41,848 miniature films, taken in 34 counties since January 1, 1947. The films of 341 students indicated suspicious heart conditions; this number comprised 0.8 per cent of the students X-rayed.

In connection with the contact program a total of 2,280 large 14 x 17 X-rays were taken over a 12-month period in 43 counties; the films of 160 or seven per cent of those examined showed suspicious heart conditions.

Only a limited number of X-rays were made at industrial plants during the past year; among the 10,179 persons examined, 116 or one per cent showed suspicious heart conditions.

In the four state mental institutions a total of 7,413 miniature X-rays were made in addition to 994 large 14 x 17 retakes and pictures of persons who could not be X-rayed with the miniature films; in this group the heart conditions reported numbered 309 or four per cent of the total. One interesting fact was noted in this connection, however. A trifle more than a third of all pathological findings noted among those examined in the mental institutions proved to be cardiac.

Although the figures quoted are for a limited period of time only, we think that, as the volume of work increases, the number of suspected heart conditions found will likewise increase.

Workers in Iowa claim no pattern or rule of thumb by which to diagnose suspected heart disease on the X-ray film. We think, however, that, even though only ten per cent of cardiac abnormalities were found by means of the chest X-ray program, we could be considered derelict in our duty as public health officers not to report these cases.

#### SUMMARY

In a state-wide program in Iowa, on a county-wide basis, conducted by the State Department of Health and the Iowa Tuberculosis Association, a total of 926 suspected heart conditions was reported as the result of taking 62,714 miniature and large chest X-rays during six months in 1946 and four months in 1947. Two-thirds of those examined were high school students.

Questionnaires were sent to physicians concerning 213 of the 341 suspicious heart conditions found among high school students; 65 per cent of the inquiries had been answered by June, 1947. Of the 213 students with suspicious cardiac abnormalities 43 per cent reported to their physicians, 22 per cent failed to report, and the remaining number (35 per cent) was not accounted for.

More than half (55 per cent) of the 92 students who reported to their physicians proved to have definite heart lesions, while the remaining 45 per cent were diagnosed as having no definite heart lesions.

#### SUMARIO

##### *Descubrimiento de Casos en Iowa*

En una obra que abarcó todo el Estado de Iowa, tomando por base todos los condados del mismo, y que llevaran a cabo el Departamento de Sanidad del Estado y la Asociación contra la Tuberculosis de Iowa, se comunicó un total de 926 corazones "sospechosos" entre 62,714 radiografías en miniatura y grandes hechas para tuberculosis durante seis meses de 1946 y cuatro meses de 1947.

Se remitieron cuestionarios a 134 médicos con respecto a 213 de los 341 casos de corazón sospechoso descubiertos en las Escuelas Superiores. Para la fecha en que se presentó este trabajo, se habían recibido 87 contestaciones que representaban 65 por ciento de los cuestionarios: 92 sujetos, o sea 43 por ciento de los investigados, se presentaron para examen; 47, o sea 22 por ciento, no se presentaron, quedando así 74, o sea 35 por ciento de los investigados, sin explicación.

De los 92 casos que se presentaron para examen, en 51, o sea 55 por ciento, había lesiones cardíacas bien definidas, y en el resto no las había.

## HEART SIZE IN FOUR BY FIVE INCH FILMS<sup>1, 2</sup>

WILLIAM PAUL THOMPSON<sup>3</sup> AND JOSEPH JELLEN

The current widespread use of miniature films in mass surveys for the detection of pulmonary tuberculosis has led to an appreciation that many abnormalities other than those of the lungs pass before the eyes of the radiologist. Among these are abnormalities in size and shape of the heart. Experience in industrial surveys in Los Angeles County has shown that such abnormalities of the heart are found in about two per cent of the films.

From the beginning of the survey program of the Los Angeles County Tuberculosis and Health Association in May 1943 through April 1947, 1,696 films were interpreted as suspicious of some cardiac disorder. Of these, 1,147 have to date been reviewed clinically and the clinical diagnosis reported to us. Cases have been referred to private physicians who have indicated their willingness to give aid to cardiac clinics, and to the diagnostic cardiac clinic organized in part for this purpose by the Los Angeles Heart Association and the Los Angeles County Tuberculosis and Health Association. Many of those not yet followed are still pending, others have been placed in the inactive file because of our inability to trace the individuals or to indifference on their part.

Clinical confirmation of our radiological suspicions in the 1,147 followed cases has been to the extent of 68.9 per cent, the remaining cases being regarded by the clinician as having normal hearts. Among those with clinical diagnoses of heart disease, 62.2 per cent had no previous knowledge of their heart disease. Thus, about one per cent of all persons surveyed in the industrial program had heart disease of which there was no prior knowledge. These people were regarded as employable by themselves or by their employers. As survey programs are broadened to include schools, hospital patients and the general population, this proportion may be expected to rise significantly.

### RECOGNITION OF CARDIAC ABNORMALITY

From the radiological point of view heart shadows reveal abnormalities in the shape or size of the cardiac silhouette. Abnormality in shape includes the aorta and its knob, the pulmonary artery, the position of the auriculo-ventricular point, the contour of the cardiac apex, and the appearance of the right lower arc. Other features of the film provide important information in cardiac appraisal; among these are the hilar shadows, the lungs themselves, and notching of the ribs.

<sup>1</sup> Presented at the Conference on Heart Disease Programs at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 16, 1947.

<sup>2</sup> This study was made under the auspices of and by the aid of a grant from the Los Angeles County Tuberculosis and Health Association. The General Electric X-ray Corporation of Los Angeles aided materially in supplying equipment, technical aid and film.

<sup>3</sup> Chairman, Heart Advisory Committee, Los Angeles County Tuberculosis and Health Association, Los Angeles, California.

Measurement of the heart presents many problems regardless of the method used. In miniature films made at short target-film distances additional problems are injected. Survey films for tuberculosis are made during full inspiration, while most prediction tables for cardiac measurement are for films made at the end of quiet inspiration. Full inspiration will usually make the transverse diameter of the heart smaller than it will be during quiet inspiration, although this is not invariably the case. Miniature films made at short target-film distances of about 43 inches introduce relative magnification of the heart as compared with teleroentgenograms made usually at a distance of 72 inches. It is considered impossible to measure the heart at such short distances. The whole matter of cardiac measurement using miniature films has therefore been subjected to study.

#### METHOD OF STUDY

Details of this study will be published elsewhere (1), a summary only being given here. X-ray films of a metal rule cut at intervals of 2 cm. were made using the standard 14 x 17 inch film at a distance of 72 inches, and using miniature 4 x 5 inch film at a distance of 43 inches. Measurements in the standard films were found to be 3.7 times greater than those in the miniature films.

One hundred ten individuals studied clinically were selected to represent small normal heart size, average normal heart size, slight, moderate and marked enlargement of the heart. Each of these groups was divided into individuals of slender build, average build and stocky build. In each individual, standard and miniature films were made at full inspiration.

On the average the transverse diameter of the heart was 3.701 times greater in the standard than in the miniature films. We have accepted 3.7 as the conversion factor when comparison is made between the two technics. Although slight magnification was noted in the case of large hearts and in those subjects of stocky build (less than 2 per cent), this was regarded as negligible. It was not, in fact, appreciably greater than the differences when multiple exposures by the same technic were made on the same subject or when stereoscopic films were made.

The cases studied lead us to believe that this method can be used as reliably for cardiac measurement as the standard 14 x 17 inch teleroentgenogram.

#### IDENTIFICATION OF CARDIAC ENLARGEMENT IN INDIVIDUAL FILMS

The conversion factor of 3.7 may be used to multiply the transverse diameter found in 4 x 5 inch films at a distance of 43 inches and the result then applied to the standard prediction tables in general use. We have modified the Ungerleider-Clark table (2) simply by dividing all transverse diameters in the table by 3.7 so that the observed transverse diameter in 4 x 5 inch films at 43 inches may be applied directly. In the use of standard tables or our modification of the Ungerleider-Clark table, survey films are made during full inspiration while the tables generally apply to films made at the end of normal quiet inspiration. Thus, a heart which appears enlarged by the table will, in fact, almost certainly be enlarged.

## THE CARDIO-THORACIC RATIO

Use of prediction tables requires that height and weight of the subject be known. It is imperative that these measurements be recorded if such tables are to be used. This entry has not usually been made in the past in our locality and in others. Because of this a study was made of the cardio-thoracic ratio, well known to be an exceedingly poor way to estimate heart size, but the only one that can be used in the great number of films already made.

When a cardio-thoracic ratio of 50 per cent was accepted as the upper limit of normal, correlation was not good. In 99 cases in which the cardio-thoracic ratio could be compared by the two technics, both the table method and the cardio-thoracic ratio agreed in indicating enlargement or lack of enlargement in 77 cases. In the remaining cases one method indicated enlargement while the other did not. It is true that several of the cases in which there was a discrepancy between the two methods, the heart was near the borderline in size, but in a few cases disagreement was conspicuous. Associations undertaking surveys must realize that the use of the cardio-thoracic ratio will omit a number of cases with cardiac enlargement and will lead to suspicion in a number of cases with normal hearts. This accounts largely for the fact that clinical confirmation of our radiological suspicions was forthcoming in only 68.9 per cent. Until this study progressed it was not clearly appreciated that height and weight are essential parts of the survey. It is true they are time-consuming, but their use will reduce the production of unnecessary anxiety on the part of many subjects, and will bring a greater yield of positive cases.

## RECOMMENDATIONS

1. That height and weight be routinely recorded during mass surveys for pulmonary tuberculosis.
2. That great care be used in centering the subject.
3. That films not be interpreted as far as the heart is concerned when rotation is present, when there is pericardial fat which cannot be clearly identified as such, or when the cardiac borders are obscured by cardiac or respiratory motion.
4. That it be clearly understood many cases of cardiovascular disease will not be detected by the use of survey films alone.
5. That a diagnosis of heart disease not be made on the basis of survey films alone, and that suspected cases be studied clinically and by the use of standard 14 x 17 inch teleroentgenograms made at the end of quiet inspiration.
6. That it be realized the radiological method is not suitable as the sole method for conducting a case-finding program for heart disease, but that it will find some cases of heart disease as a by product of surveys made primarily for tuberculosis.

## CONCLUSIONS

1. Four by five inch films made at a distance of 43 inches can be used as reliably for estimation of cardiac enlargement as standard 14 x 17 inch films made at 72 inches.



2. The transverse diameter of the heart as measured in 4 x 5 inch films at 43 inches may be multiplied by 3.7 and the result applied to standard prediction tables in general use, allowance being made for the fact that survey films are made during full inspirations, and that the tables are usually based on films made at the end of quiet inspiration.

3. The transverse diameter in 4 x 5 inch films at 43 inches may be applied directly to our modification of the Ungerleider-Clark prediction table, allowance being made for differences in the phase of respiration.

4. When height and weight are not known, a cardio-thoracic ratio of over 50 per cent will identify cardiac enlargement in the majority of instances, but a few individuals with enlargement will be overlooked and a few with normal hearts will be suspected of heart disease.

#### CONCLUSIONES

##### *Cardiometría con Películas de 10 por 12.5 Cm.*

1. Las películas de 10 por 12.5 cm. obtenidas a una distancia de 1.075 m. pueden utilizarse para estimar la hipertrofia cardíaca con igual confianza que las corrientes de 35 x 42.5 tiradas a una distancia de 1.82 m.

2. El diámetro transversal del corazón, tal como se obtiene en las películas de 10 x 12.5 cm. a 1.075 m., puede ser multiplicado por 3.7 y aplicarse el resultado a las tablas corrientes de predicción, después de tomar en cuenta el hecho de que las películas de encuesta se obtienen durante la inspiración total y que las tablas suelen basarse en las tiradas al terminar una inspiración tranquila.

3. El diámetro transversal obtenido en las películas de 10 x 12.5 cm. a 1.075 m. de distancia puede ser aplicado directamente a la modificación por el A. de la tabla de predicción de Ungerleider-Clark, después de descontar la diferencia en la fase de inspiración.

4. Cuando no se conocen la talla y el peso, una razón cardio-torácica de más de 50 por ciento identificará la hipertrofia cardíaca en la mayoría de los casos, pero se pasará así por alto a algunos cardiomegálicos a la par que se sospechará cardiopatía en algunos sujetos con corazones normales.

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# HEART DISEASE DETECTION IN PREEMPLOYMENT EXAMINATIONS<sup>1</sup>

B. E. KUECHLE<sup>2</sup>

It is somewhat presumptuous for a layman to participate in a conference on heart diseases. In declining a telegraphic invitation however, I suggested to Dr. Emerson the importance of detecting possible unknown cardiac disease in workers in order to assist in the job placement of such persons.

[You know the result—here I am.]

The American Heart Association in its pamphlet, "1 out of 3", states that one of the major unsolved problems in the field of heart diseases is the maintenance of those suffering from heart diseases as useful, productive members of society.

Industry has indicated, not only through public expression, but by actual performance, its complete willingness—yes, even enthusiasm—to employ handicapped persons. The response of disabled workers, whether handicapped by age or impaired through disabilities produced by accidents or disease, was one of the highlights of our war effort.

Not only was the production record of handicapped individuals on a very high level when compared with supposedly normal workers, but standards of loyalty, concentration on their job, lower accident rates, reduced absenteeism, were above normal expectancy.

However, no rehabilitation program worthy of the name can succeed or even be initiated unless its first phase is a well-planned medical program designed to place present or prospective employees at jobs where, in spite of handicaps, they will be able to work efficiently and safely; safely not only to themselves, but to their fellow workers and the public.

Larger industries have generally adopted medical programs of this character. In smaller industries, the necessary medical scrutiny to place handicapped persons in suitable employment is completely lacking, save in the case of obvious defects such as amputations.

Any survey programs sponsored by public or private health agencies that do not make available to industry and employees alike the maximum utilization of available medical information are not fulfilling their obligation to the fullest extent.

Industry by operation of compensation laws is required to assume the full responsibility of industrial accidents and diseases, regardless of prior infirmities, known or unknown. In some states an attempt is made through second injury funds to distribute the burden of individual cases over all industry; in the end, however, it is industry which must assume the full obligation because second injury funds are created by assessments against industry levied in certain other types of cases, usually non-dependency death claims or dismemberment cases.

The continual tendency to liberalize compensation laws through legislation

<sup>1</sup> Presented at the Conference on Heart Disease Programs at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 16, 1947.

<sup>2</sup> Employers Mutual Liability Insurance Company, Wausau, Wisconsin.

and administration will in a more plentiful employment market tend to cause discrimination against handicapped persons. This is a danger which rears its ugly head when insignificant injuries become major charges against industry because of complications and increased costs due to prior impairments.

Cardiacs can be employed and should be employed for their own well being. Out of 2,081 patients, representing the entire enrollment of 10 adult cardiac clinics in New York City, 65 per cent were doing some work, and of 543 who were under 35 years of age, 80 per cent were productively employed.<sup>3</sup>

The Heart Advisory Committee of the Los Angeles County Tuberculosis and Health Association reports that two per cent of 70,000 miniature films showed abnormal cardiac shadows. Dr. Paul White in an article in *Vogue* for May 1947 states that the X-ray is only rated at 5 per cent for diagnostic purposes in heart studies. As a clinician, Dr. White probably thinks in terms of individual cases. By the same token the X-ray might rate at only 20 per cent in the diagnosis of tuberculosis. However, as a screening or case-finding method in either heart disease or tuberculosis, the X-ray is extremely valuable particularly since it is possible to examine such large numbers of people in such a short time.

The X-ray will give suggestive or positive evidence in most cases of hypertensive or rheumatic heart disease, in many cases of arteriosclerotic heart disease and in a certain number of cases of syphilitic heart disease (aneurysms). Doctors trained in reading miniature films would be thoroughly qualified and able to recognize most of these abnormalities. It must be recognized that many cases of heart disease show no abnormality in the X-ray picture. This is particularly true where the disease is primarily of the coronary arteries without hypertension. It is also true however, that a certain number of small tuberculous shadows may be hidden behind the ribs, and hence missed on routine surveys.

We must always think of the importance of the many cases that are found in surveys rather than the few that might be missed. Therefore, in spite of the low credit which might be given to X-rays for diagnostic purposes, these individuals who are numbered among the 2 per cent are entitled to the full value of the information revealed by routine surveys made primarily for an entirely different purpose. Industry is likewise entitled to this same information—at least when proved to be of positive significance to aid in the better placement of the individual.

I do not care to discuss the mechanics of carrying out the program to its eventual application in industry, but the implications require very careful study to accomplish the possible goal through co-operative effort.

Tuberculosis associations or public health agencies cannot lull citizens submitting to routine X-ray surveys into a sense of well being by ignoring obvious or suspicious findings, regardless of their nature, merely because the study relative to pulmonary lesions is negative.

Neither can a survey program be successfully carried on that creates unjustified fears in the minds of individuals because of questionable findings which may be, and many times are, of no significance.

<sup>3</sup> "Heart Disease and Employment" by L. J. Goldwater, M.D., *Rhode Island Medical Journal*, March 1947.

## CHROMOGENIC ACID-FAST BACILLI<sup>1</sup>

Their Use in Vaccination against Tuberculosis in the Guinea Pig

WILLIAM C. WENKLE, RUSSELL N. LOOMIS AND JOSEPH M. JARBOE

It is not a rare occurrence that highly colored colonies of acid-fast bacilli appear on sputum cultures. These colonies are lemon yellow to orange in color and are smooth and glossy in growth. They may appear in pure culture, or along with tubercle bacilli. Microscopically, the organisms are acid-fast and are not unlike the tubercle bacilli in morphology. They are classified as acid-fast, non-pathogenic saprophytes. Pinner found them to be present in 0.9% of 5,000 diagnostic sputum cultures, and observed that they may occur in irregular frequency, from complete absence at times, to three or four per cent at other times. We, too, have made this same observation.

There is no known constant human source for these organisms, although they are found in cultures from sputum, nasal secretions, urine, skin and mucous membranes. They are observed in arrested or apparently cured cases as well as in active cases of tuberculosis. Other acid-fast organisms are found in nature on timothy grass, soil, dung, algae and the mud of ponds. They may be found in butter and in ordinary tap water. However, not all non-pathogenic acid-fast bacilli are chromogenic.

Pinner reported that these chromogenic bacilli produce self-healing granulomatous lesions in guinea pigs. In this respect they are not true saprophytes but are parasitic or pathogenic. Pinner also showed that guinea pigs injected with these organisms later gave a positive tuberculin skin test. He was able to recover these organisms from infected animals quite regularly up to three weeks after inoculation. We were able to recover chromogenic organisms thirty weeks after the original inoculation. It was observed by Koch and confirmed by subsequent investigators that antisera prepared against the pathogenic mammalian tubercle bacilli agglutinate the free-living, non-pathogenic acid-fast bacilli. Other workers have demonstrated cross-agglutination reactions between the various chemical fractions of the non-pathogenic acid-fast organisms and the serum from tuberculin sensitive animals. Cross sensitization reactions between tuberculin sensitive animals and the various fractions of the non-pathogenic, acid-fast organisms has also been demonstrated.

Such suggested relationships of the non-pathogenic organisms to the pathogenic organisms prompted us to try to produce immunity in the guinea pig against the virulent human tubercle bacillus by first inoculating the animals with the chromogenic organisms that we find on our sputum cultures.

### METHOD

Seventy-five normal, healthy guinea pigs were infected subcutaneously with a suspension of one-hundredths of a milligram (0.01 mg.) of chromogenic acid-

<sup>1</sup> From Olive View Sanatorium, Olive View, California.

fast organisms obtained in routine culture procedures. Our culturing is done by inoculating sputum concentrate on glycerinated egg-yolk medium. Fifteen weeks after injecting each pig with the chromogenic organisms, each animal was skin tested with 5 milligrams of Old Tuberculin. At intervals of seventeen and of thirty-six weeks after vaccination with the chromogenic organisms, each guinea pig was injected subcutaneously with varying amounts of a live, virulent strain of human-type tubercle bacilli (strain  $\times$  H-5051). At the same time thirty more non-vaccinated pigs were similarly infected, and these were to be the controls.

One month after infection with the human-type tubercle bacilli the pigs were again skin tested with five milligrams of Old Tuberculin.

From twelve to thirteen weeks after infection, the guinea pigs were killed and autopsied. The amount of tuberculosis in the glands, spleen, liver and lungs was recorded on the basis of from zero to four plus in each system.

The enlarged glands from three of the pigs were cultured on glycerinated egg-yolk media.

#### RESULTS

With an infecting dose of one ten-thousandths of a milligram (.0001 mg.) of virulent tubercle bacilli, the chromogen-vaccinated pigs developed only a fifth as much tuberculosis as the controls when the time interval between vaccination and infection was seventeen weeks. When the time interval was thirty-six weeks between vaccination and infection, and the dose of infecting tubercle bacilli remained the same, the vaccinated pigs developed only two-fifths as much tuberculosis as the controls.

When one-thousandth of a milligram (.001 mg.) of the virulent tubercle bacilli was given 36 weeks after vaccination, the chromogen-vaccinated pigs developed one-half as much tuberculosis as did the controls.

One-hundredth of a milligram of tubercle bacilli, given as the infecting dose 36 weeks after vaccination, affected the pigs the same as did the dose one-tenth as large. The pigs in this group developed only three-fifths as much tuberculosis as did the controls.

But when one-tenth of a milligram of tubercle bacilli was given as the infecting dose 36 weeks after vaccination, the chromogen vaccinated pigs developed one and two-fifths times more tuberculosis than did the controls. Here, we assume, was no protection.

All the guinea pigs reacted to tuberculin after vaccination with the chromogenic organisms, and again after infection with tubercle bacilli.

Of the three glands cultured at autopsy, all three grew tubercle bacilli, and one grew chromogens.

#### DISCUSSION

These results compare quite closely with the results Bogen and Loomis obtained by similar methods with B.C.G. and with heat-killed virulent tubercle bacilli. Irvine summarizes the literature on immunization of guinea pigs by stating that "All investigators are agreed that it is impossible completely to immunize the guinea pig against tuberculosis; the most that can be done is to

delay the progress of the disease so that the inoculated animal lives longer than the control."

It was noted that there was more tuberculosis in the group of vaccinated pigs receiving the largest dose of virulent tubercle bacilli than there was in the control group receiving the same dose. Perhaps this was an illustration of the Koch Phenomenon in which larger doses of infecting bacilli in the hypersensitive animal produce a quicker cellular response than that produced by the same infection in a normal animal. Aside from this one group, we feel that vaccination with chromogenic acid-fast organisms does confer a certain amount of immunity to the guinea pig. The amount of protection they afforded was almost identical to that Bogen and Loomis found when they experimented with B.C.G. in a similar way. Because of this, we believe that further experimentation should be done with these chromogens.

That these organisms may have clinical value in the immunization against tuberculosis in the human is only faintly implied.

But there have arisen many questions among us in regard to these organisms. Are they a mutation product of the tubercle bacillus? If so, did this mutation take place in the course of the patient's disease, or is it a mutation produced over a long period of time through many transplants from individual to individual. There are many different strains of these organisms and many degrees of virulence among them. Pinner found two virulent strains that changed to typical tubercle bacilli after serial animal passage, but no one else has succeeded in duplicating this.

On the cultures of arrested and apparently cured patients we have noted pure cultures of chromogenic acid-fast bacilli, but no tubercle bacilli. This observation has made us wonder if these people have been hospitalized for long periods of time only because of the finding of acid-fast bacilli in their sputum. Or, can these organisms in a phase of pepped-up virulence produce infiltration and ulceration? These observations and impressions need to be studied further.

#### SUMMARY

Seventy-five guinea pigs were vaccinated with chromogenic acid-fast bacilli seen frequently on the culture media at Olive View Sanatorium. After vaccina-

*Comparison of average amount of tuberculosis per guinea pig in the vaccinated and control animals with various doses of infecting virulent human-type tubercle bacilli*

DOSE REINJECTION	INTERVAL AFTER VACCINATION	AVERAGE AMOUNT T.B. PER GUINEA PIG		DIFF. CONTROL-VACCINATED	RATIO VACC. CONT.
		Vaccination	Control		
mg.	wt.				
.0001	17	0.8	4.0	3.2	1/5
.0001	36	3	7.4	3.6	2/5
.001	36	2.4	5	2.6	1/2
.01	36	5	9	4	3/5
.1	36	9	7	-2	7/5
Average . . . . .		4.0	6.5	2.5	2/3

tion, the pigs became hypersensitive to tuberculin. After infecting these vaccinated animals with various doses of a virulent strain of human-type tubercle bacilli, a definite, but not complete, immunity was produced. Vaccinated pigs receiving a massive infecting dose developed more tuberculosis than did the controls receiving the same dose.

#### SUMARIO

##### *Vacunación Anti-Tuberculosa del Cobayo*

A 75 cobayos se les vacunó con bacilos ácidosresistentes cromógenos de los observados frecuentemente en los medios de cultivo del Sanatorio Olive View. Después de la vacunación, los cobayos se volvieron hipersensibles a la tuberculina. Después de infectar a esos animales vacunados con varias dosis de una cepa virulenta de bacilos tuberculosos de tipo humano, obtúvose inmunidad bien definida, pero no absoluta. Los cobayos vacunados que recibieron una dosis infectante masiva manifestaron más tuberculosis que los testigos que recibieron la misma dosis.

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# AGE SPECIFIC SUSCEPTIBILITY TO TUBERCULOSIS<sup>1, 2</sup>

Experiments on Guinea Pigs and Rats

CHARLES J. DUCA<sup>3</sup>

Age is generally considered one of the factors in susceptibility to tuberculosis. Experimental evidence on the subject has been conflicting or open to question (1). Koch (2), Wakushima (3), and Smithburn (4) found that young animals are more resistant to experimental tuberculosis than are older animals, while Gartner (5), Kleinschmidt (6), Laporte (7), and Perla (8) found the reverse. Other workers on this problem, including Baumgarten (9), Maffucci (10), Uffenheimer (11), Wright and Lewis (12), Krause (13), and Kuster and Kroning (14) found no significant difference between young and old animals in their susceptibility to experimental tuberculosis. Gerstl and Thomas (15) found that mice between 20 and 50 days old showed more resistance than younger or older mice. Rich (1) has examined most of the work cited above and has shown that little of it yields unequivocal evidence.

In the following study an attempt was made to acquire information on the relation between the age of guinea pigs and of albino rats and their susceptibility to experimental tuberculosis.

## EXPERIMENT 1

In this experiment 69 guinea pigs were used. At the time of infection 9 were newly born, 20 were 4 weeks old, 20 were 1.5 years old, and 20 were more than 4 years old. Average weights at these ages were: newborn, 86.3 gm., 4 weeks old, 267 gm., 1.5 years old, 829 gm., and 4+ years old, 916 gm. All (except the newborn group) reacted negatively to 1 mg. O. T. (Mantoux) before infection, which consisted of 0.01 mgm. *M. tuberculosis bovis* (B<sub>1</sub>) per 500 gm. body weight, injected subcutaneously in the region of the right groin.

All animals were tested weekly with 1 mgm. O. T. by the Mantoux method. Weekly blood lymphocyte-monocyte ratios were done on the members of the 3 older groups. They were all autopsied within 12 hours of death, the amount of gross disease in the lungs, liver, spleen, and lymphatic system was noted, and the spleen was weighed. From the latter the spleen-body weight ratio was calculated. Histological sections were made of the four organs, and were examined for type of disease and numbers of tubercle bacilli encountered.

## RESULTS

### 1. *Survival time*

The survival times of the four groups are depicted in Chart I, the vertical lines on the base marking the average survival times of the different groups. This

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shows that there was no significant difference in the rate of dying between the three older age groups. The 4 week olds had an average survival time of 169.9 days, the 1.5 years olds 158.4 days, and the 4+ years olds a survival time of 159.7 days. When the differences in survival time are tested statistically (16), *P* in all cases is greater than 0.1, indicating that the differences are not significant. But the new born group had an average survival time of 62 days. When compared with the older groups by the method cited above, *P* is much smaller than 0.01, indicating that the differences found are not the result of chance.

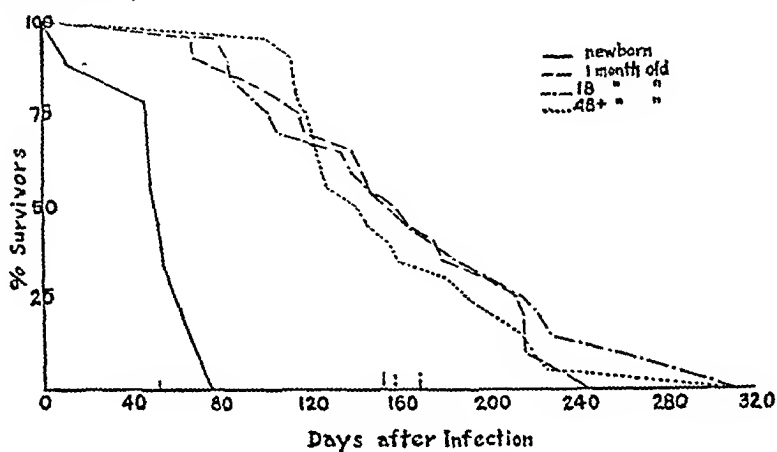


CHART I. EXP. 1. Survival times of guinea pigs of different ages after subcutaneous infection with .01 mg. *M. tuberculosis bovis* (*B<sub>1</sub>*) per 500 gm body weight.

## 2. Lymphocyte-monocyte ratio

No difference was found between the three groups at any time during the course of the infection.

## 3. Tuberculin tests

In the three older groups, no difference was observed in the reactions to intradermal tuberculin, all the guinea pigs in these groups yielding positive skin reactions 7-10 days after infection. The new born group did not react to 1 mgm. O. T. subcutaneously until 2 weeks after infection, and the first positive reactions in this group were weaker and smaller than those observed in the older groups.

## 4. Spleen-body weight ratio

When the results of these determinations were analysed statistically (16), no significant differences were found.

## 5. Pathology

An attempt was made to follow the progress of the disease by palpation of the regional lymph glands. No differences between the four groups could be detected by this method.

Table 1 shows the average gross tuberculous disease in the various organs as found at autopsy. Extensive generalized involvement of an organ is denoted by 4+, while minimal involvement, consisting usually of a few discrete lesions, is denoted by 1+.

Inspection of this table shows an apparent difference in the amount of disease between the newborn and the older groups, but when this is tested statistically, the difference is significant only in glandular involvement,  $P$  in this case being 0.01. Among the older groups, the differences in organ involvement have only slight significance statistically,  $P$  in all cases being close to 0.05. However, the basis upon which these results are obtained is so subjective that the statistical analysis must be accepted with great caution.

TABLE 1  
*Autopsy findings in guinea pigs of different age groups*

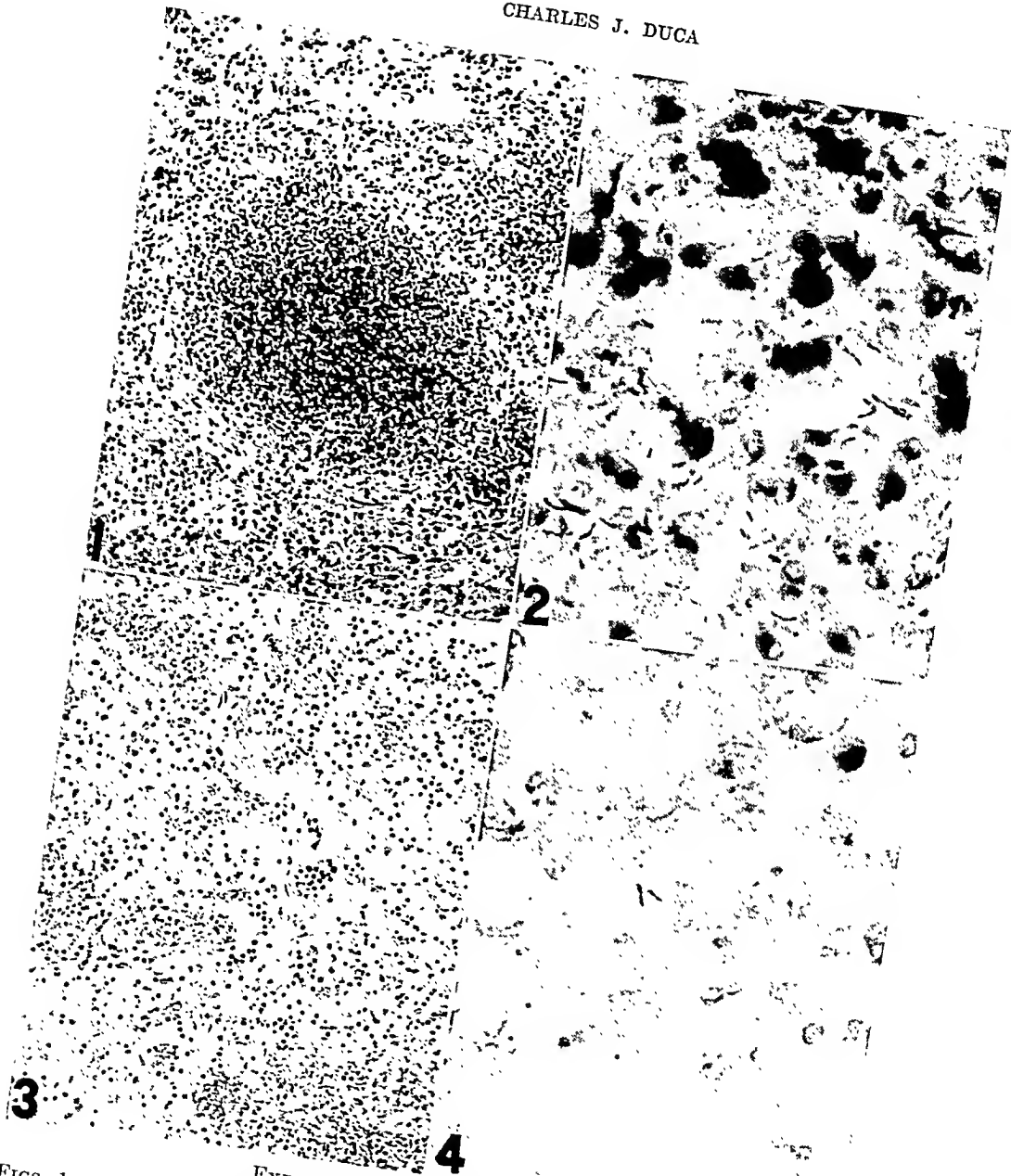
AGE	NUMBER	LUNGS	LIVER	SPLEEN	GLANDS
Newborn	9	2.7	2.0	2.5	2.4
4 weeks	20	3.3	2.7	3.3	3.3
1.5 yrs.	20	2.8	2.6	2.4	3.3
4+ yrs.	20	2.7	2.5	2.8	3.8

When representative sections were examined, no differences were found between the three older groups. Lesions were nearly all somewhat fibrotic, with caseous centers and abundant cellular reaction consisting mostly of epithelioid cells, with lymphocytes and a few polymorphonuclears. Tubercle bacilli could be found in all the sections, being most abundant at the periphery of the caseous material. No differences in numbers of acid fast bacilli were noted between these three groups. But in the newborn group the histological picture differed from the others in that the lesions were of the exudative type, with much caseation, little fibrosis, and heavy cellular reactions which were loosely organized. Large numbers of acid fast bacilli were present. The cells were almost exclusively monocytes and epithelioid cells. This whole picture sums up to an acute exudative process. Indeed, the cause of death in 5 of the 9 animals of the newborn group could be said to be tuberculous pneumonia. Sections of the lungs of one of the newborn and one of the 1.5 year group are illustrated in Figs. 1-4.

## EXPERIMENT 2

Since the results of Experiment 1 indicate that greater susceptibility is found only in the very early days of a guinea pig's life, another experiment, using a greater number of newborn animals, was performed in order to obtain more evidence.

For this purpose, 29 pregnant guinea pigs were obtained, 15 from Montefiore Hospital and 14 from this institution. They were closely watched, and as soon as a newly born litter was found, one of the young was infected with tubercle bacilli. Another of the litter was infected 15 days after birth, and another 30



#### EXPERIMENT 1. Guinea Pig Lungs

FIGS. 1 AND 2. Newborn guinea pig #61 died 49 days after infection.  
 FIG. 1 Mag.  $\times 150$ . Hematoxylin-eosin stain.  
 FIG. 2. Mag.  $\times 1200$ . Ziehl-Neelsen stain.

FIGS. 3 AND 4. 18 month guinea pig #28 died 148 days after infection.  
 FIG. 3. Mag.  $\times 150$ . Hematoxylin-eosin stain.  
 FIG. 4. Mag.  $\times 1200$ . Ziehl-Neelsen stain.

days after birth. The total number of guinea pigs born was 84, the average number per litter being 2.6. Of these, 22 died before or shortly after infection, leaving 62 which died with at least 2+ tuberculosis. These were distributed

among the three age groups as follows: newborn, 28, 15 days old, 18, and 30 days old, 16. At these ages the guinea pigs weighed as shown in table 2.

All of the 15 and 30 day old guinea pigs were negative to 1 mgm. tuberculin injected intracutaneously the day before infection. They were all infected in the same manner and with the same dose of the same strain of bovine tubercle bacilli as was used in Experiment 1. The animals were tested weekly with 1 mgm. tuberculin by the Mantoux method, until all reacted. All animals were autopsied as soon as possible after death, and the amount of gross disease in the lungs, liver, spleen, and lymphatic system was noted. Portions of the four organs were removed to Zenker's solution, sectioned, and stained with hematoxylin-eosin and Ziehl-Neelsen stains. The sections were examined for type of lesion and numbers of acid fast bacilli encountered.

TABLE 2

	gm.	average
Newborn	40-100	71.6
15 days	138-229	162.5
30 days	165-280	227.5

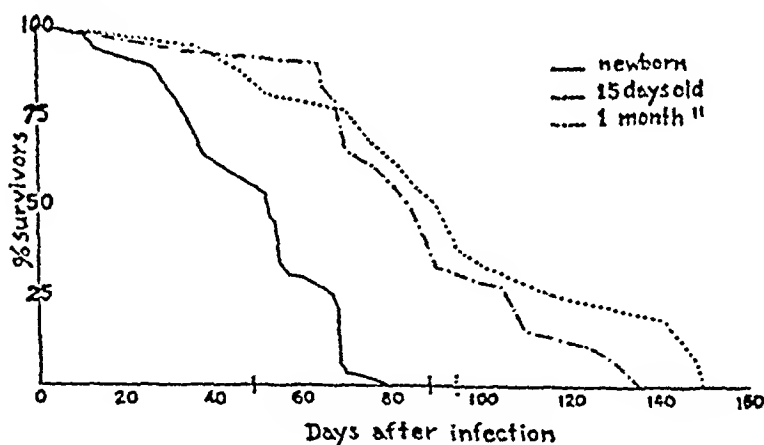


CHART II. Exp. 2. Survival times of guinea pigs of different ages after subcutaneous infection with .01 mg. *M. tuberculosis bovis* ( $B_1$ ) per 500 gm body weight.

## RESULTS

### 1. Survival time

The survival times of the three groups are depicted in Chart II. Average survival times are denoted by the vertical marks on the base line. For the newborn group this was 48.7 days, for the 15 day group, 88.7 days, and for the 30 day group, 95.6 days. When the differences in survival times were tested statistically (16), it was found that the difference between the two older groups is of no significance. But when the survival time of the newborn group was tested against the older groups, either separately or together, or against the general

survival time of all the animals (72.4 days), the differences in survival times were found to be of great significance,  $P$  in all cases being much smaller than 0.01. When the survival time of the 30 day old group of Experiment 1 was compared statistically with that of the same age group in Experiment 2, the difference was found to be of no significance,  $P$  being greater than 0.1.

## 2. Tuberculin tests

The results of the tuberculin tests in this experiment were the same as in Experiment 1. The newborn group was about a week later in reacting to 1 mgm. tuberculin intracutaneously than the older groups, which reacted first about 10 days after infection.

## 3. Pathology

As in the previous experiment, no difference could be detected in the course of the disease between the different age groups by means of palpation of the regional lymph glands.

TABLE 3  
*Autopsy findings in guinea pigs of different age groups*

AGE	NUMBER	LUNGS	LIVER	SPLEEN	GLANDS
Newborn	28	2.7	3.2	3.3	2.8
15 days	18	3.0	3.7	3.7	3.0
30 days	16	2.0	3.1	3.6	3.3

Table 3 shows the average tuberculous disease in lungs, liver, spleen, and lymphatic system of the groups as found at autopsy. The method of scoring was the same as in Experiment 1.

Inspection of this table shows no great differences in amount of disease between the various groups.

Most of the differences have little or no statistical significance. When the glands of the newborn group were compared with those of the 30 day group,  $P$  is 0.05. When the livers of the newborn group are compared to those of the 15 day group,  $P$  is greater than 0.01, as is the case when the lungs of the 30 day group are compared with the lungs of the two younger groups. Caution must be used in accepting the results of statistical analysis when the statistics are collected on so subjective a basis.

When sample sections of the various organs were examined microscopically, the findings of Experiment 1 were confirmed. The type of lesion in the two older groups was the same as is described for the older groups of Experiment 1. In the newborn group the type of lesion was again more exudative. This was most clearly seen in the pulmonary lesions. About two-thirds of the newborn animals showed a more or less widely spread bronchopneumonia characterized by congestion, patches of alveoli filled with an exudate consisting almost entirely of large mononuclears, often surrounding an earlier tuberculous lesion,

and not infrequently with spots of caseation necrosis in the pneumonic areas. The alveolar walls were perfectly intact; even the caseous areas being sharply delimited by them.

This type of lesion was present in greater or less intensity in 18 of the 28 in the newborn group, while it was found in only 5 of the 34 guinea pigs in the two older groups. The pulmonary condition in the 18 of the newborn group was probably a major factor of the cause of death.

The number of acid fast bacilli found in the lesions of the various groups varied widely, but they could always be found if the section were carefully searched. The numbers of bacilli present in the pneumonic areas also varied from occasional ones, the finding of which required persistent search, to literally thousands per oil immersion field. The extremely large numbers of acid fast bacilli were found especially in and around the caseous pneumonic areas, though large numbers of bacilli could often be found on the periphery of the caseous material in other types of tuberculous lesions. No clear differences could be detected between the numbers of acid fast bacilli found in the different groups.

### EXPERIMENT 3

Since the guinea pig is relatively extremely susceptible to tuberculosis, a study of experimental tuberculosis in very young individuals of a normally resistant species might provide further information on the question of age susceptibility to this disease.

### MATERIALS AND METHODS

Two groups of rats were obtained, from stock bred in this institution, there being 15 in each group. Group I was 5 days old at the time of infection, Group II was 35 days old when infected. They were all infected intracardially with 0.1 mgm. per 100 gm. body weight of bovine tubercle bacilli ( $B_2$ ) (moist weight). Tuberculin tests (Mantoux), employing 1 mgm. as the dose, were done weekly for the first month after infection.

At five intervals, namely 1, 30, 60, 90, and 200 days after infection, three rats in each group were sacrificed. The rats were autopsied with complete precautions for sterility, and the lungs, liver, spleen and kidneys were removed to sterile Petri dishes. They were then weighed, and a small portion removed for histological study. The rest of the organ was then thoroughly ground in a sterile mortar with sterile sand. When the tissue was reduced to a smooth pasty consistency, a suitable amount of sterile  $M/15 Na_2HPO_4$  was added and well mixed. The entire material, now in suspension, was then centrifuged lightly to throw down the sand and coarse particles. Aliquot portions of the supernatant fluid from each organ were then removed and seeded onto three tubes of Petragnani's medium. These tubes were kept in the incubator for 24 hours in a horizontal position so that the fluid could evaporate, leaving any solid particles evenly distributed over the surface of the slant.

The cultures were incubated for six weeks, during which time precautions were taken to assure an adequate amount of moisture. They were closely watched,

and as soon as colonies could be clearly seen, smears were made to check the presence of acid fast bacilli, and the total number of colonies was counted, with the aid of a 5 $\times$  hand magnifying glass. The number of colonies found in the three tubes was averaged, and the result used to calculate the number of organisms isolated from each gram of the particular organ studied. Culture done in this manner of the emulsion used for infection showed an average of 2,000,000 viable bacilli per mgm. (moist weight).

At the time of autopsy, the amount of gross disease was noted, and the histological sections were studied for type of reaction and relative numbers of bacilli seen.

### RESULTS

Tuberculin tests were at all times negative or doubtful, the latter consisting of small swellings without erythema or induration. The doubtful reactions occurred only a few times and only in the older age group.

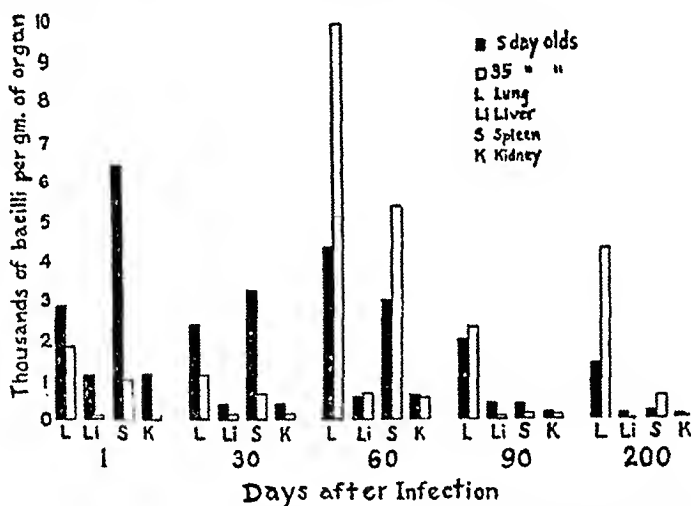


CHART III. EXP. 3. Thousands of bacilli cultured per gram of different organs from rats of different ages infected intracardially with 0.1 mg. *M. tuberculosis bovis* (B<sub>1</sub>) per 100 gm body weight.  
TB 5264 p. 2

The average numbers of tubercle bacilli cultured from the various organs of the two age groups are given in Table 4, and are illustrated in Chart III.

Inspection of these shows consistent differences to be present only in respect to the kidneys, for which the young rats had a higher proportional content of tubercle bacilli throughout the course of the experiment. The figures obtained on the first and thirtieth day after infection show that the younger rats at these times had many more bacilli in all the organs tested than did the older group. From sixty days until the end of the experiment the number of bacilli per gram of lung was higher in the older group of animals. The numbers of bacilli per gram of liver differed only slightly sixty days after infection, but at 90 and 200 days the

younger rats showed more bacilli in this organ than did the older rats. In the spleen the group having the higher count alternated, the older group being highest at 60 and 200 days, while the younger group had the higher count 90 days after infection. The lungs and spleen, therefore, in which experimental tuberculosis is usually found in the intravenously infected rat, show greater numbers of organisms for thirty days after infection in 5 day old rats than they show in rats infected when 35 days of age. But in the liver and kidneys, which are not noted as sites of infection in experimentally infected rats, the count is higher in the younger animals throughout the experiment except in the case of the liver 60 days after infection, where the counts are virtually equal. After 30 days of infection the older rats show higher counts in the lung, while during this period the highest number in the spleen alternated between younger and older groups.

TABLE 4

*Numbers of bacilli cultivated per gram of organ in rats of different age groups*

DAYS AFTER INFECTION	LUNGS		LIVER		SPLEEN		KIDNEYS	
	5 day old rats	35 day old rats	5 day old rats	35 day old rats	5 day old rats	35 day old rats	5 day old rats	35 day old rats
1	2800	1784	1243	134	8890	735	1483	699
30	2414	1137	274	112	3281	727	421	237
60	4314	9930	494	512	2989	5400	620	466
90	2000	2333	477	14	415	138	80	8
200	1406	4320	31	0	180	550	50	15

Each figure is the average of 5-9 cultures from 3 rats.

### *Pathology*

Study of tissue sections stained with the Ziehl-Neelsen stain and with hematoxylin eosin showed no marked difference between the two groups. The younger rats showed a slightly more intense reaction, and in their lesions polymorphonuclears were more frequently present, especially in the lungs and spleen. The course of the infections in both groups of rats was substantially the same as has been described (17, 18).

The number of bacilli seen in the sections did not differ between the two groups, and did not show any constant relation to the number found by culture.

### DISCUSSION

The experiments described above clearly show that in guinea pigs, a significant increase in susceptibility is to be found only in the first days of life, for 15 day old guinea pigs responded to a standard infection with tubercle bacilli in exactly the same manner as did animals of all the older groups. Probably the different tissue reaction of the newborn group was responsible for the decreased survival time, and the different tissue reaction may be related to the delayed development of sensitivity to tuberculin found in this group. Allergy would tend to hinder the spread of small inocula, such as was used in this case, and was present



in the older groups a week earlier than in the newborn. In the latter group, therefore, a larger proportion of the inoculum reached the lungs, liver, and spleen, as was found in the experiment with rats.

The presence of relatively large amounts of tuberculo-protein in a sensitive tissue could well explain the type of lesion found in the newborn guinea pigs. In the rat, on the other hand, the insignificant role played by allergy in tuberculosis of this species (17) probably explains why the younger rats reacted to a standard infection with tubercle bacilli in the same manner as the older rats, even though the former group yielded greater numbers of bacilli on culture of their organs in the first thirty days of infection.

Another possible factor contributing to the difference between the newborn and older groups may be the relative inability of young individuals to produce antibodies in response to antigenic stimulation. This has been shown to be true with a large number of antigens including bacteria, viruses, protozoa, and helminths (8), and this may well be the case with the tubercle bacillus, although the role played by antibodies in resistance to tuberculosis is not at all clear (1). Experimental proof of this would be difficult, since it would be necessary to use an animal with a suckling period as long as a human's.

While no experimental evidence is available on the question of age susceptibility to tuberculosis in humans, a great mass of clinical and statistical observations shows that the highest case mortality from tuberculosis is found in the first year of life (1). Since the guinea pig is at least as different from the human as it is from the rat, it is impossible to extend findings in the experimental animal to man. Therefore the present study cannot help to elucidate the problems connected with the high case mortality in the human infant. It does indicate that important and interesting problems connected with age susceptibility, such as the effect of vaccination of the very young, should not be performed with guinea pigs, since the interval during which age differences can be found in this species is so short. Experiments planned to solve problems of natural resistance to tuberculosis in humans should use species close to humans in the scale of evolution, and with periods of infancy much longer than the few weeks found in rodents.

#### CONCLUSIONS

1. The newborn guinea pig is more susceptible to experimental tuberculosis than are pigs 15 days, or 1, 18 or 48 months of age. This fact is shown by the marked decrease in survival in the former group and by the more acute and progressive type of tuberculosis found at autopsy.

2. No differences in susceptibility to experimental tuberculosis are found in guinea pigs 15 days, or 1, 18 or 48 months of age. This finding is shown by the lack of difference in survival time in these groups. They all showed the same type of fibrocaseous tuberculosis, more chronic in character than that found in the suckling group.

3. The 5 day-old rat is slightly more susceptible to experimental tuberculosis than the 35 day-old rat. The organs of the 5 day-old rats contain proportion-

ately more bacilli in the early stages of the disease than are found in the organs of older rats.

### CONCLUSIONES

#### *La Edad y la Susceptibilidad Específica a la Tuberculosis*

1. El cobayo recién nacido es más susceptible a la tuberculosis experimental que el de 15 días, o de 1 mes, o 18 ó 48 meses de edad, según revela la pronunciada disminución de la sobrevivencia en el primer grupo y la forma más aguda y evolutiva de tuberculosis descubierta en la autopsia en el mismo.

2. No se encuentran diferencias en la susceptibilidad a la tuberculosis experimental en los cobayos de 15 días, o de 1, 18 ó 48 meses, según revela la igualdad del tiempo de sobrevivencia en esos grupos. Todos revelaron también la misma forma de tuberculosis fibrocásica, más crónica que la observada en el grupo lactante.

3. La ratilla de 5 días es un poco más susceptible a la tuberculosis experimental que la de 35 días. Los órganos de las ratas de 5 días contienen proporcionalmente más bacilos en los períodos incipientes de la enfermedad que los órganos de ratas más viejas.

The author wishes to express his sincere gratitude to Dr. M. M. Steinbach, College of Physicians and Surgeons, Columbia University, for his constant advice and encouragement.

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## ACID-BASE CONDITION IN TUBERCULOSIS<sup>1,2</sup>

H. S. KOLMER, D. ELLIS, T. SMITH, P. COLLINS AND E. M. GREISHEIMER

### INTRODUCTION

For some time we have been interested in the acid-base condition in the serum of patients with fever. The advent of therapy with sulfonamides, penicillin, streptomycin and other antibiotics has limited the number of untreated fever patients available for study, and confined our investigation largely to patients with tuberculosis.

Few reports of the acid-base condition of the blood in patients with tuberculosis are available. Wiese (1) in 1936 studied the hydrogen ion concentration of the blood in 45 patients with pulmonary tuberculosis. He found the range of pH of the blood to be 7.27 to 7.40, with no extreme variations from the normal of 7.40. He found no correspondence between the pH of the blood and the physical condition of the patient and consequently considered the pH of no diagnostic or prognostic value.

Winkler and Crankshaw (2) in 1936 observed a range of 50.6 to 66.8 volumes per cent of plasma bicarbonate concentration in 14 cases of pulmonary tuberculosis. The plasma chloride concentration varied from 87 to 103 m.eq. per liter. The concentration of sodium in the plasma was determined in 3 cases; the values found were 119.6, 125.2 and 126.1 m.eq. per liter. In one case, the chloride and sodium concentration of the plasma remained low in spite of the administration of large amounts of sodium chloride, and in spite of the absence of vomiting, diarrhea or excessive sweating. This is just the opposite of the condition seen in the hypochloremia of pneumonia, in which there is almost complete retention of administered sodium chloride with very little urinary excretion of either sodium or chloride. In tuberculosis large amounts of sodium chloride were excreted in the urine even though the concentration of both sodium and chloride in the serum remained low. The chloride deficit was not correlated with the severity of the disease nor the extent of the lesion. This chloride depletion results from the ability of these subjects to excrete chloride readily in the urine at levels of serum chloride at which normally urinary excretion of the ion virtually ceases.

Thorn et al. (3) in 1940 investigated a series of 103 tuberculous patients with special reference to Addison's disease. The serum chloride concentration ranged from 84 to 102 m.eq. per liter. The carbon dioxide content varied from 49 to 72 volumes per cent; the concentration of sodium in the serum varied from 135.5 to 151.0 m.cq. per liter, with a mean value of 139.7. The extent of the tuberculous infection had no significant effect on the serum sodium concentration. This finding substantiated the idea that the low serum chloride concentration was in large measure the result of a reciprocal shift in the concentration of the anions Cl and HCO<sub>3</sub>. The concentration of serum potassium was not elevated. There was a slight decrease in the pH of serum of arterial blood.

<sup>1</sup> From Temple University School of Medicine, Philadelphia, Pennsylvania.

<sup>2</sup> Sharp and Dohme supplied funds to defray a part of the expense of this study.

We thought it worth while to study a large number of patients with tuberculosis and to compare the results so found with those obtained from an equally large group of relatively normal individuals.

#### METHODS

The blood was collected under oil (by use of a tourniquet) several hours after breakfast, in most cases. All determinations were made on serum of venous blood. pH determinations were made by glass electrode at 38°C. in a cell which permitted only minimal exposure to air. The carbon dioxide content was determined by the Van Slyke manometric method. The chloride concentration was determined by the open Carius method.

The concentration of total base in the serum was determined by the resin method developed by Polis and Reinhold (4), and slightly modified by us. With each group of determinations duplicate controls were run on a standard solution of sodium chloride which contained 100 m.eq. per liter. The recovery varied from 99 to 105% in all cases.

#### RESULTS

##### *I. Comparison of patients with tuberculosis with normal individuals*

The acid-base condition of the serum was investigated in 92 patients with tuberculosis; they were all young adults. There were 35 women and 57 men in the group. The results found in this group will be compared with the results found in a group of 109 normal individuals. Determinations on 62 men and 47 women (at the midpoint of the menstrual cycle) are included.

(a) *Chloride concentration:* The range of the serum chloride concentration in patients with tuberculosis was 76 to 105 m.eq. per liter, with a mean of 91.68 and the standard deviation was 6.38. The range of the serum chloride concentration in the normal individuals was 88 to 105 m.eq. per liter, with a mean of 99.19 and a standard deviation of 2.90. The standard error of the difference between the means was 0.734. The chloride concentration is significantly lower in patients with tuberculosis than in a comparable number of normal individuals. This is shown by the fact that the difference between the means (7.51) is ten times greater than the standard error of the difference between them.

The decrease in chloride concentration is not peculiar to the febrile condition associated with tuberculosis; it has been reported in other clinical fevers, as well as in experimental hyperthermia and fever therapy (5, 6, 7 and 8).

(b) *Total base concentration:* The range of total base concentration in the serum of patients with tuberculosis was 127 to 171 m.eq. per liter, with a mean of 153.66 and a standard deviation of 7.88. The range in normal individuals was 148 to 173 m.eq. per liter, with a mean of 158.35 and a standard deviation of 4.56. The standard error of the difference between the means was 0.94. The concentration of the total base in the serum of the patients with tuberculosis is significantly lower than in normal individuals. The difference between the means (4.69) is about five times greater than the standard error of the difference between them.

A brief review of the results found by several investigators since 1930 will be given. In many cases the individual cations were determined and the sum compared with total base by various methods. Sunderman (9) in 10 normal subjects found the sum of sodium, potassium, calcium and magnesium in serum to be between 144.6 and 148.8 m.eq. per liter, and the total base by the method of Stadie and Ross (10) varied from 142.0 to 149.3 m.eq. per liter. Hald (11) converted the bases to sulfates and used the benzidine method; she found the total base average in 10 individuals to be 146.5, and the sum of the cations to be 145.8 m.eq. per liter. Butler and MacKay (12) found a mean total base of 157 m.eq. per liter by the method of Van Slyke, Hiller and Berthelsen (13). Keys (14), using the method of Adair and Keys (15), found the total base to be between 151.4 and 168.8, and the sum of the cations to be between 150.8 and 169.2 m.eq. per liter. Hald and Eisenman (16), with the gravimetric benzidine method found the total base varied between 139 and 150, and the sum of the cations between 139.9 and 149.8 m.eq. per liter. Leva and Guest (17), devised a new method for total base, and found values which ranged from 149.3 to 158.6, while the sum of the cations ranged from 152 to 157.9 m.eq. per liter. Consolazio and Talbott (18) with an improved electro dialysis method found values which compared favorably with the gravimetric, Van Slyke and Hald methods. Consolazio and Dill (19) found sodium concentrations of serum which ranged from 138 and 142 m.eq. per liter, by the method of Butler and Tuthill (20), modified by them. Hald (21) used radioactive sodium and found a range in serum of 134.2 to 141.0, with an average of 137.1 m.eq. per liter; she feels that the higher values obtained by other workers are due to inaccuracies in procedures. It will be noted that the question of methods of determining total base of the serum is still an open one.

(c) *Carbon dioxide content*: The range of carbon dioxide content in the patients with tuberculosis was 54 to 78 volumes per cent, with a mean of 65.9. The range in the group of normal individuals was 56 to 79 volumes per cent, with a mean of 66.5. There is no significant difference between the two groups. The range found in both compares favorably with that of 59.6 to 71.5 found by Cullen and Robinson (22) in the plasma of normal individuals.

A decrease in the serum carbon dioxide content in clinical fever, experimental hyperthermia and fever therapy has been reported by many authors (5, 6, 7, 8, 23, 24, 25 and 26). In these cases, hyperventilation was prevalent and undoubtedly responsible for the lowering of the carbon dioxide content. Peters (5) suggested that the reduction of bicarbonate concentration which usually occurs with elevation of temperature may be prevented in pneumonia by impairment of the respiratory mechanism; perhaps there is likewise an impairment in pulmonary tuberculosis which prevents the blowing off of carbon dioxide by hyperventilation.

(d) *pH*: The range of pH in the serum of patients with tuberculosis was 7.18 to 7.55, with a mean of 7.37. The range of pH in the serum of the group of normal individuals studied was 7.27 to 7.45, with a mean of 7.36. Cullen and Robinson (22) found a range of 7.28 to 7.41 in plasma pH in a group of normal individuals.

Some of the difficulties attendant upon collecting blood at one temperature

and determining the pH of its serum at another temperature were pointed out by Stadie et al. (27). They found that true serum, which was separated from cells under equilibrium conditions and kept so that no loss or gain of carbon dioxide could occur, assumes a new equilibrium with consequent change in pH, on change of temperature. The initial values of pH, carbon dioxide content and base bound with protein influence the change in pH with change in temperature. Austin and Cullen (28) developed equations by which one could calculate the

TABLE 1

*Moderately advanced tuberculosis*

Range and mean values of pH, CO<sub>2</sub> content (in volumes per cent), chloride concentration (in m. eq. per liter) and total base concentration (m. eq. per liter) in serum

SUBGROUP	pH	CO <sub>2</sub> CONTENT	CHLORIDE CONC.	TOTAL BASE CONC.
A (7 cases)	7.39 (7.36-7.43)	67.3 (67-68)	89.1 (83-93)	162.3 (158.6-167.4)
B (5 cases)	7.39 (7.30-7.45)	67.7 (65-72)	92.5 (85-98)	159.4 (150.2-171.0)
C (4 cases)	7.29 (7.23-7.36)	66.0 (65-69)	91.4 (89-95)	151.2 (144.0-156.8)

TABLE 2

*Far advanced tuberculosis*

Range and mean values of pH, CO<sub>2</sub> content (in volumes per cent), chloride concentration (in m. eq. per liter) and total base concentration (m. eq. per liter) in serum

SUBGROUP	pH	CO <sub>2</sub> CONTENT	CHLORIDE CONC.	TOTAL BASE CONC.
A (14 cases)	7.35 (7.25-7.43)	65.1 (56-77)	95.1 (87-100)	156.9 (147.5-169.5)
B (17 cases)	7.36 (7.26-7.49)	66.6 (59-73)	92.4 (77-104)	156.1 (144.6-165.6)
C (15 cases)	7.38 (7.28-7.55)	65.9 (57-78)	89.7 (78-105)	152.3 (138.8-162.7)

initial pH of febrile blood or of blood from chilled or heated extremities, from its pH at 38°C., and its carbon dioxide content. A change in temperature of blood at constant CO<sub>2</sub> or BHCO<sub>3</sub> causes a marked change in pH and little change in pOH. Since we failed to note the temperature of the patient at the time of collection of the sample we are unable to apply the essential corrections to the pH readings made at 38°C. However, since it has been the custom in the past to make all pH determinations of blood at 38°C., our results may be compared directly with those reported in the literature. It is realized that these values may

not apply to the actual hydrogen ion activity at the average temperature of the blood in the tuberculous patient with fever.

An elevation in plasma or serum pH in clinical fevers, experimental hyperthermia and fever therapy has been reported by many authors (6-8, 23-26). In these cases hyperventilation was present and the observed shift in pH probably indicates a simple respiratory alkalosis and not a response to fever per se.

It seems that in the chronic fever associated with tuberculosis there is neither an acidosis nor an alkalosis. We agree with Wiese (1) that the serum pH as

TABLE 3

*Mean daily temperature*

Mean daily temperature based on all temperature recordings each day during the week preceding the study. The chloride concentration and the total base concentration are expressed in terms of milliequivalents per liter

TEMPERATURE		NO. OF CASES	CHLORIDE CONC.		TOTAL BASE CONC.	
Mean	Range		Mean	Range	Mean	Range
°F.						
97.6	97.0- 97.9	24	93.0	82.9-104.7	160.0	150.2-171.0
98.4	98.0- 98.9	22	90.6	88.1- 99.0	155.3	144.6-167.4
99.4	99.0- 99.9	15	89.9	79.1- 98.4	150.0	140.6-162.7
100.4	100.0-100.9	6	84.8	77.3- 90.2	147.4	138.8-153.0

TABLE 4

*Mean maximal daily temperature*

Mean maximal daily temperature based on the maximal temperature for each day during the week preceding the study

TEMPERATURE		NO. OF CASES	CHLORIDE CONC.		TOTAL BASE CONC.	
Mean	Range		Mean	Range	Mean	Range
°F.						
98.4	98.0- 98.9	33	93.7	82.9-104.1	158.6	145.8-171.0
99.4	99.0- 99.9	13	93.8	88.1- 98.4	152.5	144.6-160.9
100.4	100.0-100.9	12	87.0	79.1- 91.9	149.2	140.6-162.7
101.5	101.0-101.9	6	87.1	77.3- 97.2	147.5	144.0-161.1

measured does not inform one as to the physical condition of the patient, and is of no diagnostic or prognostic importance.

## II. The Acid-base condition of the serum in relation to classification

In the group of 92 tuberculous patients, it was possible to secure the classification in 62 cases; of these, 16 were in the moderately advanced and 46 in the far advanced class. The results found in each class, with its subgroups, are shown in Tables 1 and 2.

In the moderately advanced group, the only definite change is a consistent decrease in the mean total base concentration as one progresses from subgroup A

through B and C. In the far advanced group, the mean chloride concentration decreases from subgroup A through B and C. However, one notes no striking correlation between the clinical classification and decrease in chloride or total base concentration.

### *III. Chloride and total base concentration in relation to temperature variations*

The data were studied in relation to the body temperature variations of the patients during the week preceding the sampling. The mean daily temperature, the mean maximal daily temperature and the mean daily fluctuations in temperature were determined when available. Since the serum pH and carbon dioxide content seemed uninfluenced by the level of body temperature they will be omitted. The results found for serum chloride and total base concentrations are presented in Tables 3, 4 and 5. It appears that the patients who have higher mean daily temperatures, higher maximal temperatures and greater daily fluctu-

TABLE 5

#### *Mean daily fluctuations*

Mean daily fluctuations of temperature based on the fluctuation for each day during the week preceding the study

TEMPERATURE		NO. OF CASES	CHLORIDE CONC.		TOTAL BASE CONC.	
Mean	Range		Mean	Range	Mean	Range
<sup>°F.</sup>						
0.72	0.0-0.9	17	93.0	84.9-99.0	158.9	149.4-169.5
1.19	1.0-1.4	26	93.2	84.6-104.7	155.2	140.6-165.5
1.65	1.5-1.9	15	91.5	78.1-103.3	154.5	144.0-171.0
2.23	2.0-2.9	9	86.5	77.3-96.1	146.7	144.2-154.8

ations have, in general, lower concentrations of chloride and total base in their sera than those patients whose temperatures vary less from the normal range.

### DISCUSSION

The question of the significance of fever to the human body has been a puzzling one for a long time. Does one develop immunity more efficiently at an elevated body temperature? By what means does fever therapy benefit some conditions? In other conditions it seems advantageous to the patient to lower the body temperature. Is the tuberculous patient with the greatest elevation of temperature putting up the best fight against the infection, or is this high temperature the indication that he is putting up no fight, and losing the battle? So far as our studies go, the patients with the most marked elevations and fluctuations of temperature show the greatest depletions of serum chloride and total base and yet show pH values and carbon dioxide contents within the range of normal individuals. Why are the former constituents affected more than the pH value and carbon dioxide content?

The chloride depletion is not peculiar to tuberculosis. The fact that the



chloride concentration remains low, in spite of the administration of large amounts of sodium chloride, in the absence of excessive vomiting and sweating, differentiates tuberculosis from certain other hypochloremic conditions, in which administered sodium chloride is retained. Perhaps this indicates a difference in kidney function, since tuberculous patients excrete sodium chloride at serum levels at which normal individuals retain it (2). A thorough study of kidney function by recent clearance methods might help us solve this difficulty.

The loss of total base in tuberculous patients may be due to the same mechanism which is concerned with chloride depletion.

In most conditions accompanied by elevated temperatures there is such an increase in respiration that carbon dioxide is blown off, leading to respiratory alkalosis. However, in tuberculosis, in spite of an elevated temperature, the respiratory mechanism is not stimulated, therefore the carbon dioxide content remains within the normal range. Perhaps there is an impairment of the respiratory mechanism, as has been suggested in pneumonia (5).

The pH value, which proves so helpful in diagnosis, prognosis and as a guide to therapy in many varied conditions, gives us no information on which to base decisions in tuberculosis.

Since complete studies of the acid-base condition in the serum of patients with tuberculosis are so rare, we undertook this investigation for two reasons; in the first place, we wished to add to the limited information available along this line; in the second place, we attempted, in vain, to clarify some of the questions in the broad field of fever. It is difficult to find febrile patients in whom therapy is not aimed directly at lowering the temperature, except in institutions for tuberculous patients, therefore, our two purposes were admirably united in this investigation.

#### SUMMARY

1. We have studied the acid-base condition of the serum in 92 patients with tuberculosis. The results are compared with those of a similar study in 109 persons in good health.

2. The serum chloride concentration is significantly lower in patients with tuberculosis.

3. The total base concentration is significantly lower in patients with tuberculosis.

4. There is no significant difference in the carbon dioxide contents in the two groups.

5. There is no significant difference in the pH of the serum of the two groups. Since the pH in separated serum undergoes changes with change in temperature, one can draw no conclusions from pH determinations made on serum from blood drawn from febrile patients and read at 38°C.

6. There is no striking correlation between the classification of the tuberculous patient and his acid-base condition. One cannot determine the classification from the acid-base condition.

7. The patients who experience higher degrees of fever, with greater daily fluctuations, show lower concentration of serum chloride and total base than those whose temperature deviates less from the normal range.

## SUMARIO

*Estado Acido-Básico del Suero en los Tuberculosos*

1. En este estudio del estado ácido-básico del suero en 92 tuberculosos, compárase el resultado con el obtenido en 109 personas sanas.
2. En los tuberculosos la concentración de cloruro sérico es significativamente menor.
3. En los tuberculosos la concentración de bases totales también es significativamente menor.
4. No hay mayor diferencia en el contenido de bióxido de carbono en los dos grupos.
5. No hay mayor diferencia en la pH del suero entre los dos grupos. Dado que la pH en el suero separado manifiesta alteraciones al variar la temperatura, no cabe sacar conclusiones de las determinaciones de la pH, realizadas en suero de sangre extraída a enfermos febriles y leídas a 38°C.
6. No existe correlación notable entre la clasificación del tuberculoso y su estado ácido-básico, y por éste no puede determinarse aquella.
7. Los enfermos que manifiestan fiebre más alta, con mayores fluctuaciones diarias, revelan una concentración de cloruro sérico y bases totales menor que aquellos cuya temperatura se desvía menos de la escala normal.

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# TUBERCULOUS LARYNGITIS<sup>1</sup>

## A Controlled Study

JOHN PAUL MYLES BLACK

Since the middle of August, 1946, 60 patients with laryngeal tuberculosis have been followed in a controlled therapeutic study. In the beginning the cases were classified according to the laryngeal disease as mild, moderately severe and severe. Alternate cases were chosen for the various types of treatment to be used. A series of 20 cases received promin; 10 cases received penicillin; 30 cases received ultra-violet rays and/or cautery or simply general sanatorium treatment.

All patients treated were under sanatorium care for pulmonary tuberculosis. The pulmonary disease in all cases was moderately or far advanced. In the larynx the predominant lesion noted was inflammation and edema. In a few cases ulceration was visible and in 17 cases granulations were noted. The extrinsic larynx was involved in the largest number of cases. The distribution of lesions is as follows: 10 on the epiglottis, 46 on the arytenoids, 51 on the posterior commissure, 40 on the false cords and 29 on the true cords. There was an even distribution of the various type lesions for the different forms of treatment.

The ratio of men to women was 15 to 40. This series does not include all the cases of tuberculosis of the larynx in the Sanatorium. The ratio of all cases is 1 to 2. The ratio of men to women in the Sanatorium is 1 to 1. Most of the observations were made on patients in the 18 to 35 age group. The dosage of promin used was 0.5 g. daily; that of penicillin was 100,000 units daily. The amount of solution for daily application was limited to 6 to 8 cc. daily. The solution was delivered to the diseased areas with the use of a DeVilbiss spray. The applications were made six times daily from 7 a.m. to 7 p.m. In an effort to determine the efficiency of the spray several patients were chosen to use a methylene blue solution in the DeVilbiss spray. By this method it was noted that the dye reached all portions of the extrinsic and intrinsic larynx. Some of the dye was present as far down the trachea as could be seen with a laryngeal mirror. The initial applications were made under supervision. After that the technique was corrected at regular intervals if necessary. The ultra-violet radiation treatments were given three times weekly. The cautery was used when the indication arose.

The observations were made in four periods: 23 August to 1 October; 2 October to 25 December; 26 December to 1 March; 2 March to 25 April. The number of patients in each treatment period varied because new or different forms of treatment were instituted in some cases where the disease was progressive with the original treatment and facilities for the other treatment available. Laryngoscopic examinations were made biweekly and the findings recorded graphically, and evaluated independently at the end of each treatment period.

From Olive View Sanatorium, Olive View, California.

Altogether 20 cases received promin, 10 cases received penicillin and 30 cases were observed as controls. By this time, 4 of the promin cases have cleared completely; 3 of the penicillin cases cleared and 2 of the control cases are listed as having no active disease. Both of the cases in the control cases received ultra-violet radiation in erythema doses. Six of the promin cases, one case on penicillin and 6 in the control series showed improvement. No change was seen in 3 of the promin series, one of the penicillin series and 4 of the controls. Progression of the disease occurred in 7 promin cases; 2 of these patients died. In one there had been an initial good response to the drug, but as the patient became moribund and the cough reflex was diminished, the laryngeal lesions became worse. In the other case the promin had been used for a period of six weeks with no response. The lesion here was a large ulcer of the epiglottis with associated edema of the entire extrinsic larynx. Severe dysphagia was not controlled by nerve injection, the patient rapidly lost weight and died. The pulmonary disease was not severe enough to cause death at this time. Five cases on penicillin showed progression as well as 18 controls; 5 of these controls died. In 2 of these the death was attributable to the laryngeal and intestinal disease.

The only toxic manifestations noted were two severe allergic reactions to penicillin. These were controlled with benadryl 50 mg. but the treatment had to be discontinued. In the promin group there was an initial drop in the hemoglobin in all cases. After the initial drop the hemoglobin remained at a stationary level around 70 per cent in spite of transfusions in some cases and routine iron therapy.

The lesions treated with promin showed the greatest response initially. Usually much of the edema and inflammation subsided in a period of two to four weeks. After that the granulations, roughness of mucosa and residual edema gradually subsided where there was continued improvement. In 2 patients with granulomatous lesions, there was no response. In 2 other cases of severe destruction of the epiglottis promin had no effect. One of these cases had been mentioned previously as one who died, following six weeks of therapy.

In the final tabulation of results 20 cases were treated with promin. 10 with penicillin and 30 cases were observed as controls receiving only ultra-violet rays and in a few instances cautery.

	PROMIN	PENICILLIN	U. V. AND CAUTERY
Healed.....	4	3	2
Improved.....	6	1	6
Unchanged.....	3	1	4
Worse.....	7	5	18
Total.....	20	10	30

The mode of action of the two sprays was largely a cleansing action to the solution bathing the larynx. This conclusion was made when the first change

noted in the appearance of the diseased larynx was a cleaner mucosa, even though inflamed and edematous. The cleansing action in itself would influence the presence of secondary invaders. The specific antibacterial action of penicillin would also reduce the element of secondary invaders and in turn help to increase local tissue resistance. The promin theoretically will act against secondary invaders as well as against the acid-fast bacilli. In the laboratory it can be shown that promin has a bacteriostatic and bactericidal effect on the tubercle bacillus.

At the present time additional studies are being carried out on the use of local and systemic administration of streptomycin and the local use of a mixture containing one gram each of streptomycin and promin in a 2 per cent solution of trypan blue. The results of these studies leave no doubt that adequate streptomycin treatment is more effective than any other measure so far introduced.

#### CONCLUSIONS

Both promin and penicillin therapy in tuberculous laryngitis were beneficial. They did not, however, produce satisfactory results in all cases, especially not in some very severe forms. They were more valuable than other routine forms of therapy and should be tried if streptomycin therapy is not available.

#### CONCLUSIONES

##### *Estudio Comprobado de la Laringitis Tuberculosa*

En la laringitis tuberculosa tanto la promin como la penicilino-terapia resultaron beneficiosas. Sin embargo, no dieron resultado satisfactorio en todos los casos, y en particular en algunas formas muy graves. Fueron sí más útiles que otras terapéuticas corrientes y deben probarse si no hay estreptomicina a mano.

# EMPIRE CONFERENCE ON TUBERCULOSIS (LONDON) AND INTERNATIONAL CONGRESS FOR MICROBIOLOGY (COPENHAGEN)<sup>1</sup>

A Brief Report of Impressions in Post-War Europe

HENRY STUART WILLIS<sup>2</sup>

The National Tuberculosis Association asked me to represent it, along with Drs. Esmond R. Long, Rene J. Dubos and H. Corwin Hinshaw at the meeting of the Empire Conference on Tuberculosis in London and the International Congress for Microbiology in Copenhagen. Transportation schedules were such as to allow me to visit several countries and to look briefly into the situation as regards tuberculosis in these areas. Herein is presented a brief report of these experiences. The trip took me into the Scandinavian countries, and into France, Belgium and Great Britain. As did Doctors Long and Hinshaw, I presented a paper before the meetings in London and Copenhagen. One was a summary on the status of the work on streptomycin, and the other, a brief report of the work of the Committee on Medical Research of the National Tuberculosis Association and related ventures in research in tuberculosis.

*Norway:* In Norway the National Association, under the direction of Dr. T. Gedde-Dahl, appears to be flourishing, with an active interest being shown especially in case finding and preventive work by BCG vaccination. Norway's death rate for last year was near 50 per 100,000. Three particular developments deserve mention in describing the antituberculosis work in this country. They are:

1. The BCG work of Johannes Heimbeck and others.
2. Dahl's epidemiological study of a community of 6,000 for ten years.
3. Legislation in respect to compulsory vaccination with BCG.

1. For years Heimbeck has vaccinated every other nonreacting candidate for nurses training in several hospitals in Oslo and now has records which show that more than ten times as many cases of tuberculosis develop among those not vaccinated as among their vaccinated colleagues. The demonstration now rests on such firm foundation that he no longer withholds the vaccination from any nonreacting nurse.

2. For longer than ten years Dahl has repeated the tuberculin test annually on all nonreactors who were members of a stable community of 6,000. The result is that, in the large percentage of those who develop tuberculosis, the disease shows itself within a year or two of the time when its bearer became tuberculin positive. It is his belief, shared by most Scandinavian authorities on tuberculosis, that most clinical tuberculosis develops directly and rather promptly from

<sup>1</sup> Sent as a letter to Dr. Kendall Emerson, Managing Director, National Tuberculosis Association.

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the primary infection. He is, therefore, not satisfied with the division into primary and reinfection tuberculosis.

3. The National legislative body is working on a bill to require BCG vaccination of everyone fifteen years of age or less who does not react to tuberculin—this against the advice of the physicians on whose work the law is based.

*Sweden:* Sweden had about 4,000 deaths from tuberculosis last year which gave a rate of 59. The latter is dropping steadily in all groups but, as in the United States, the decline is much slower in the older age groups. The Country has 10,000 beds for tuberculosis, but some of these serve for domiciliary care only.

There is legislative proposal for free transportation of patients to dispensaries and free hospitalization for all tuberculous patients.

The Association is active in conducting extensive mass case-finding surveys on a voluntary basis. These have in some instances resulted in films on 99 per cent of the people in the community. There are plans afoot to endeavor to have the government X-ray one-fifth of the total population every year, until all have been so examined. The Association has sponsored universal X-raying of people in special occupational groups, particularly domestic servants, children's nurses, workers in industry. This survey project to date reveals tuberculosis in 0.5 per cent of all people so studied. The hope is expressed that the Association may continue to sponsor demonstrations of new lines of endeavor and, once they are established, turn them over to official agencies. Just now, case-finding, BCG immunization among contacts and rehabilitation are prominent among the activities. Last year 12,000 contacts received BCG through this agency.

Work with p-Amino-salicylic acid—PAS—has reached considerable proportions. Dr. J. Lehmann of Gothenburg has done extensive chemical work to refine the formula and obtain a compound which produces desirable clinical effects. He has used the drug on from 100 to 125 cases of tuberculosis. One of three cases of tuberculous meningitis recovered and is now free from symptoms after "several" months. Numerous cases of acute pulmonary tuberculosis appear to have cleared under PAS about as such cases do under streptomycin in our country. Little evidence of the use of controls was at hand. A thorough study of this drug should be undertaken in U. S. A., possibly in conjunction with the study of streptomycin now going on under the aegis of the Committee on Therapy of the American Trudeau Society and the Tuberculosis Study Section of the Public Health Service.

*Denmark:* No contact was made with the National Association of Denmark, but I had an opportunity to see the BCG work carried out under the auspices of the State Serum Institute, and some of the investigative work of Dr. K. A. Jensen at the University of Copenhagen. Under Dr. Johannes Holm's direction large numbers of Danes who do not react to tuberculin have been inoculated with BCG which, it is claimed, offers about 80 to 90 per cent protection; i.e. there is 7 or 8 times as much tuberculosis among the nonvaccinated as among the vaccinated in comparable age groups. Holm and his associates managed to vaccinate the entire personnel of the Danish underground during the occupation and to carry this protection to almost every Dane in German concentration and prisoner



of war camps in spite of the close German supervision but without detection.

Jensen's laboratory studies with streptomycin and other bacteriostatic and bacteriocidal drugs are interesting and promising.

The Conference on Microbiology was, as would be expected from its title, a meeting that considered many different aspects of science, medicine included. There were several papers on tuberculosis, in addition to those by the four representatives of the National Tuberculosis Association.

*France:* In France the death rate from tuberculosis at war's end is reported to have been about 400 per 100,000 and to stand now at 200. Reliability of these data is probably to be questioned.

Two developments are in progress that are particularly interesting. One is the work with streptomycin, especially that by Prof. Bernard at Laennec Hospital who presented data on nearly 200 patients with a wide range of clinical tuberculosis. In general the results tended to correspond with and to confirm those already reported in U. S. A. The other is the widespread use of extrapleural pneumothorax which in several different quarters seems almost to have superseded other important forms of collapse therapy, while this form of treatment is used now relatively rarely in the United States.

*Belgium:* The Belgian National Organization for Defense Against Tuberculosis is again very active after five years of suppression by the German occupation—which is described in an interesting, recently published brochure of 125 pages. During these years the Nazis destroyed, damaged, requisitioned or caused the evacuation of 1507 beds. They also requisitioned and thus vacated several hundred beds in preventoria. At the end of the war roughly 2,300 beds or 50 per cent of the total for the state were out of service. This situation is being resolved rapidly and new beds are under construction. New beds are needed, for 6,489 deaths were reported in 1945. This represents a rate of 81 per 100,000.

The Belgian Seal Sale has gone on the rocks. The special Christmas seal is purchased not from the Association but from the National Post Office. Although such a system is beyond the control of the Association and beyond the range of its management, it has heretofore yielded handsome support. Last year, however, the Postal authorities decided that the revenue from this seal sale must be divided among six different voluntary, benevolent organizations. This decision has demoralized the work, and no decision had been made at the time of our trip as to whether there would be a seal sale in 1947.

Active work is proceeding in case-finding, but a lurking fear of the diagnosis and the marked social stigma that appears still to attach to the disease contribute adversely to wide-spread acceptance of this scheme. This surprises one in view of the fact that the preventorium idea enjoys great popularity in Belgium. Messrs. Legai and Chauffort of the Central Office of the National Organization were extraordinarily liberal with their time, for they discussed many aspects of the work with me.

*The British Isles:* It seems unfortunate that in the tuberculosis work in this Country the educational, publicity and fund raising organization and the medical

organization should be almost totally separated from each other. There is a good deal of overlapping among the directors,—with several leaders in one being active also in the other: but the National Association for the Prevention of Tuberculosis has its own meetings, conducts its own campaigns and schedules without great regard to the meetings, schedules, etc., of the British Tuberculosis Association which concerns itself solely with medical problems. Between the two organizations cordial relationships appear to exist, but no sense of need of a close integration of interests and activities presented itself to the observer, except for the Association's sponsorship of regular meetings of Sanatorium Matrons for the discussion of administrative and professional (nursing) problems.

This is unfortunate in many ways and particularly just now when a newly formed committee on Medical Research is in need of funds to support research but is without resources. The chairman of the Research Committee invited me to attend one of its meetings in which was revealed a very forward looking, enlightened research program in the making. Contact with this association by this committee for the purpose of eliciting support is being planned. The Association maintains close contact with the government's developing Health Service Act. It supports a promising study on psychic aspects of the disease and certain studies in the colonies. It also supports country wide efforts at mass X-ray survey, social welfare work and interest in sanatorium design and construction, among many other interests.

The Government is sponsoring a systematic study of streptomycin through the Medical Research Council which is making rapid strides in the conduct of controlled observations, something on the order of those in this country under the aegis of The American Trudeau Society, The National Tuberculosis Association, the Veterans Administration and the Study Section of the United States Public Health Service. Those who are making these studies are particularly active in carrying out further observations on streptomycin in tuberculous meningitis, which disease claims many lives. Data from the Vital Statistics Service indicate that, for the four years 1941 through 1944 inclusive, there was an average of 2,499 deaths per year from meningitis in England, Wales and Scotland. This represents about 12 per cent of all tuberculosis deaths in these areas. In the United States for that same period the deaths from tuberculous meningitis averaged per year only 1,126, representing about 4 per cent of all tuberculosis deaths. It is obvious that the meningitis deaths in England, Wales and Scotland are very much in excess of those in the United States.

Doctor Hinshaw presented his clinical data to good effect before a group of the most interested in this study.

The Empire Conference in London represented essentially the Diamond Jubilee of organized work against tuberculosis in Britain. It was featured particularly by the show of an enlightened and progressive attitude on the part of those responsible for the tuberculosis work at home and in the Dominions. Much could be written about the situation presented for each Dominion. Suffice it to say, however, that case-finding, improvement in methods of treatment, provision of more beds and the judicious use of BCG vaccination predominated

throughout the discussions and stood forth as having high priority among the objectives of the workers.

In England it was my privilege to visit Dr. R. C. Brock whose work has done so much to show segmentation of the lungs and has pointed the way to effective surgical removal of segments rather than entire lobes or lungs when conditions warranted. A visit to Dr. V. E. Negus was likewise very stimulating for I was able to learn more of his work on the cilia—a subject that has sadly lacked attention in our country. Attention to these tissues could well keynote many studies in respiratory physiology.

And finally there was Papworth. This institution is hospital, sanatorium, hostel, colony and workshop. Patients graduate progressively through these stages finally to live with their families in the colony and work in the industries maintained by the organization. They work part or full time, earn an hourly rate that is fixed with the unions and comparable to the prevailing rate for the industry. The industries earn a profit.

Among the industries, printing, carpentry, cabinet making and leather work predominate. Last year more than 60,000 pieces of luggage were manufactured at Papworth. About 600 workers are employed and 175 houses are occupied by the workers. But it gave one a start to learn that an occasional employee worked in the shops and lived in the colony with his family although his sputum contained tubercle bacilli—a scheme that would meet with great disfavor in our country. He has been taught to safeguard others, and the resident physician offered evidence of the safety of the situation by saying that no case of tuberculosis had developed among the more than 200 children of the colony and that 70 children brought up in the colony had served through the rigors of a long war and had returned well (save for 2 who were killed). Papworth is a most unique organization.

It was my privilege to observe many interesting social reactions to the war and its aftermath, especially in Britain where a grim struggle still prevails, and where a great people are paying daily a heavy war cost—but such is not properly a part of this report.

I should like to thank the Association for according me the opportunity to make this trip.

COMMENTS ON MARY DEMPSEY'S ARTICLE ON "DECLINE IN  
TUBERCULOSIS: THE DEATH RATE FAILS TO TELL  
THE ENTIRE STORY"

THOMAS N. E. GREVILLE<sup>1</sup>

The TUBERCULOSIS ABSTRACT for November, 1947 was so interesting to me that I looked up the original article entitled *Decline in Tuberculosis: The Death Rate Fails to Tell the Entire Story*, by Mary Dempsey, in the August, 1947 issue of the AMERICAN REVIEW OF TUBERCULOSIS, particularly because of my concern with the use of life tables upon which the article is based.

The author's point is well taken that the seriousness of various causes of death as public health problems cannot be adequately judged on the basis of comparative death rates alone, without some consideration of the potential years of life lost, since, from the standpoint of society, the death of a person in the prime of life constitutes a greater loss than the death of one of advanced years. However, the introduction of a concept such as the potential years of life lost raises certain logical questions which can easily lead to confusion, and when such figures are presented, it is essential that the underlying assumptions be clearly stated. Unfortunately, Miss Dempsey has not succeeded in avoiding some of these logical pitfalls; and, since her method is likely to be widely imitated by other investigators desirous of quoting similar figures for other diseases, it seems desirable to point out some of the difficulties involved.

Miss Dempsey has arrived at the assumed average number of years of life lost by those dying at a given age by merely subtracting the age at death from the expectation of life at birth. For example, according to the life table used, the expectation of life at birth for a white female is 69 years, and she concludes (page 158) that a white woman who dies at age 24 has lost 45 potential years of life. She apparently realized that this is not strictly correct, for she states, on page 160, "to be more nearly accurate the potential years of life lost by persons who die of tuberculosis should be computed on the basis of life expectancy at the actual age at death . . . for reasons of expediency this more exact method of computation did not prove feasible." However, she apparently underestimated the magnitude of the error thus introduced, although this is readily apparent on inspection of the life table used, as illustrated in table 1.

These figures indicate that Miss Dempsey's method of calculation results in substantial understatement of the potential years of life lost, and that this understatement is greater in the case of deaths from cancer and heart disease, the majority of which occur at relatively older ages than those due to tuberculosis. It is difficult to guess what could have been the "reasons of expediency" which prevented Miss Dempsey from using the more exact method of computation, since the 1944 life table of the Metropolitan Life Insurance Company, to which

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she refers, gives the values of the expectation of life over the entire age range from birth to age 80, and there is no appreciable difference in the amount of arithmetical work involved under the two methods. As an illustration, I have recomputed by the more correct method the potential years of life lost by white males dying in 1944 of heart disease, cancer and tuberculosis. In these computations, I have used the deaths in 5-year age groups throughout, except that ages under 1 and 1-4 were treated separately. The expectation of life at birth was used in connection with the deaths of infants under 1 year of age; that for age 3

TABLE 1

*Comparison of different methods of computing years of life lost by white females dying at specified ages: United States, 1944*

AGE AT DEATH	EXPECTATION OF LIFE AT BIRTH <sup>a</sup>	YEARS REMAINING FROM EXPECTATION AT BIRTH (COL. (2) - COL. (1))	LIFE TABLE EXPECTATION OF LIFE FOR AGE AT DEATH <sup>a</sup>	DIFFERENCE (COL. (4) - COL. (3))
1	2	3	4	5
	years		years	
25	69	44	48	4
45	69	24	30	6
65	69	4	14	10
70	69	-1 <sup>b</sup>	11	12

<sup>a</sup> Source: Metropolitan Life Insurance Company, *Statistical Bulletin*, May 1946, 27, 3.

<sup>b</sup> Miss Dempsey does not state how she dealt with the deaths of white females occurring at ages above 69, where her method would apparently give a negative figure for the potential years of life lost.

TABLE 2

*Potential years of life lost by white males who died of specified cause: United States, 1944*

CAUSE	POTENTIAL YEARS OF LIFE LOST BY THOSE WHO DIED OF SPECIFIED CAUSE IN 1944	
	Figures published by Miss Dempsey	Recomputed figures
Heart disease.....	979,107	2,872,839
Cancer.....	393,948	1,065,079
Tuberculosis.....	422,513	624,265

was used for the age-group 1-4; and for subsequent age-groups, the expectation of life used was the mean of the values for the two ages constituting the boundaries of the age-group. For ages above 80, for which the 1944 life table of the Metropolitan Life Insurance Company does not give the values of the expectation of life, the corresponding figures from the 1939-1941 United States Life Tables were used, since there has been no appreciable change in mortality rates at these ages. Table 2 gives the results of the computation. It will be noted that tuberculosis drops from second to third place among the three causes of death as a result of the recomputation, and that the loss in potential years of life due to

heart disease which had been indicated as slightly more than twice that due to tuberculosis now appears to be more than four times as much. On the other hand, tuberculosis still looms larger in importance than when comparison is made on the basis of the crude death rate of white males which, for heart disease, is almost nine times as high as for tuberculosis.

The method used in obtaining the recomputed figures in the table, while more correct than that described in the article, still involves a certain logical inconsistency. Had it been possible to prevent all the deaths from tuberculosis which occurred in 1944, presumably the same methods could be applied to eliminate all deaths from this cause in all subsequent years as well. However, this would have the effect of reducing the total mortality rate at each age, and therefore of increasing the expectation of life at each age. This suggests that the expectations of life to be used in computing the potential years of life lost due to a given disease should be taken, not from the general life table, but from a special life table calculated on the assumption that the given disease has been eliminated as a cause of death. Such special life tables eliminating tuberculosis were published in the volume *United States Life Tables 1930*, and similar 1930 tables for all the three causes of death considered by Miss Dempsey apparently were computed by Dublin and Lotka in connection with the material presented in Chapter 6 of their book, *Length of Life*, but the life tables themselves are not shown. The authors, however, indicate that the increase in expectation of life at birth of white males that would have resulted, in 1930, from eliminating each of these causes is 2.41 years for heart disease, 1.12 years for cancer, and 1.10 years for tuberculosis. As age-specific mortality rates for heart disease and cancer have increased since 1930, while those for tuberculosis have declined, the increase in expectation of life based on 1944 mortality would be higher for the two former diseases and lower for the latter. Therefore, if this further correction could be made in the computation of potential years of life lost, the effect would be to decrease still further the relative importance of tuberculosis, as compared with heart disease and cancer.

On the other hand, it may perhaps be argued with some justice that greater importance should be attached to the loss of a year of life falling in the active period of life than to a year lost during the latter part of the life span. The selection of any fixed age as terminating the active period of life is of necessity somewhat arbitrary; however, for purposes of general comparison, it would seem not unreasonable to choose age 65, and to compute the potential years of productive life lost prior to age 65. This would require the tabulation of the values of the "expectation of active life," both on the basis of the general life table and of the special life tables eliminating certain causes of death. A study along these lines would be of considerable interest and, of course, a comparison on the basis of this criterion would tend to emphasize the importance of tuberculosis as a cause of death.

## EDITORIAL

### Tuberculosis in Europe

A number of recent publications have given impressive pictures of the tuberculosis problem in post-war Europe. Prior to 1939, tuberculosis had been steadily decreasing in prevalence in most parts of Europe for many years. The incidence varied in different countries according to the strength of the campaign against tuberculosis and other factors (1). Death rates were between 40 and 50 per hundred thousand population in Denmark and the Netherlands, between 50 and 100 in Germany, England and Wales, Belgium, Scotland, Sweden, Italy, Switzerland, Norway and Lithuania, and between 100 and 150 in Austria, Latvia, Eire, Spain, Czecho-Slovakia, Greece, France, Bulgaria, Hungary and Portugal. In Russia, Estonia, Roumania, Poland, Turkey and Yugoslavia the reported rates exceeded 150. Before the outbreak of World War II there was every reason to expect further decline in the British Isles, the Netherlands, Belgium, Germany, the Scandinavian countries, Italy and Switzerland. The rate in France, although decreasing, remained surprisingly high, and excessive rates still prevailed in Central Europe and the Balkans. The last recorded rates for Russia were also high, but current reports from the Soviet Republic indicate a vigorous control campaign, which might be expected to reduce the death rate sharply.

With the outbreak of war it was immediately evident that a setback in tuberculosis control measures was inevitable. Medical and non-medical personnel were withdrawn from sanatoria and dispensaries to fill the ranks of the rapidly growing armies, leaving these institutions badly undermanned, and at the same time certain sanatoria were converted into hospitals of a different type. This was particularly conspicuous in England, where sanatoria were emptied, and their patients sent home, to make room for expected air raid casualties. Everywhere, in the urgency of military preparation, the emphasis on tuberculosis control measures began to decline.

As the war progressed, tuberculosis control steadily deteriorated in most countries. England, fortunately, was an example of the contrary. Air raid casualties, although appalling in the aggregate, required less hospitalization than was expected, so that many of the sanatoria evacuated at the outbreak of hostilities, were restored to use as tuberculosis institutions. But, in the rest of the fighting countries, the care of the tuberculous lessened, while growing difficulties of existence, and particularly increasing malnutrition favored increase of the disease. Astonishing efforts were made in some countries to preserve the program, but in most of them a breakdown finally occurred. The extraordinary tenacity of the Germans was remarkable; a nation-wide mass X-ray survey, in progress at the beginning of the war, was carried forward until late in 1943, when continuous bombing, with destruction of equipment and disruption of organization, made it no longer feasible.

At the end of the war a profound change had taken place in the sanatorium structure of the countries which had been the seat of military operations. In

Italy the Germans took over Italian sanatoria for military hospitals. When these were captured by British and United States troops, they remained as military hospitals under new management. Not infrequently the allied medical staffs shared facilities with pre-existing tuberculosis organizations, but in general there was a great reduction in the availability of beds for tuberculosis, and remaining institutions, not requisitioned for military hospitals, like the Forlanini Institute in Rome, were severely overcrowded.

In France, Belgium and the Netherlands similar conditions prevailed. Scores of hospitals were taken over by the Germans, and in turn, retained as military hospitals when overrun by the victorious allies. In Germany, at the end of the war, hospital care was chaotic. Hospitals everywhere were crowded with wounded German soldiers, victims of bombing and displaced personnel of every sort, who wandered over the country with the dissolution of the German armies. Long before this, the exclusion of open cases of tuberculosis from German industry, once rigidly practiced, had ceased. It was reported by allied Army intelligence officers that tuberculous patients in the German population were forced to work in factories, but this appears to be in error as far as general practice was concerned. German civilians with open tuberculosis were permitted to work in industry, but not compelled, according to responsible authority.<sup>1</sup> German scientific propaganda went to great lengths to convince the public that prewar views on the contagiousness of open tuberculosis were exaggerated. However, regardless of the policy for German citizens, the number of tuberculous prisoners of war from the Eastern front and displaced personnel from all parts of Europe, who were working in industry, mining and agriculture at the end of the war, was tremendous.

United States armies in their march across the Saar and into Germany overran scores of hospitals crowded with tuberculous patients of non-German origin. One American hospital, the 46th General, housed in barrack buildings in eastern France, at one time had more than a thousand tuberculous patients, chiefly Russians, almost all of them in far advanced stages of the disease. These were but a pitiful residue of many thousands who had worked out their lives under duress, with incredibly long hours of labor, in the German mines and factories.

In the concentration camps of Germany tuberculosis ran riot. Hundreds of rotting naked bodies were found in the court yards of these evil institutions when they were captured by allied troops. These unburied, uncremated remains, left behind in the Nazis' retreat, constituted only an infinitesimal fraction of the concentration camp deaths. On the railroad from Buchenwald to Dachau scores of flat cars packed with dead bodies of former concentration camp inmates were left on sidings, some so overfilled that bodies spilled over the sides and lay neglected along the tracks. How many of these poor derelicts died of tuberculosis can never be known, but that a large number of the deaths were due to tuberculosis there can be no doubt. At Buchenwald, Dachau, Belsen, Nordhausen and other camps where some records were kept, hundreds of tuberculous patients

<sup>1</sup> Personal communication to the writer in 1945 by Prof. I. E. Kayser-Petersen, former General Secretary of the Reichs Tuberkulose-Ausschuss.



were taken out when the camps were liberated and placed in hastily improvised allied hospitals, many of them so near death that they expired within a few days, their fate differing from that of the other thousands in the camps only in that it occurred after the liberation instead of before.

Conditions in these camps were ideal for the propagation and transmission of tuberculosis. Indeed tangible evidence of the prevalence of tuberculosis in the camps was left in the pathological museums of the camp hospitals, where numerous mounted specimens of tuberculous lungs from camp autopsies remained on the shelves.<sup>2</sup> At the Belsen camp (2) British medical officers found a high incidence of tuberculosis among patients hospitalized for all causes after the liberation. Pulmonary tuberculosis in an advanced stage was clinically obvious in about six per cent of admissions. Radiological examination of unselected groups from various divisions of the hospital indicated that the total incidence of pulmonary tuberculosis, including cases of undetermined clinical significance, might be as high as 20 per cent. Active tuberculous disease was a frequent finding in the lungs of inmates who died of starvation. Physicians in some camps, who were able to record their own experience after they were freed, stated that tuberculosis was very common. Rosencher (3), in an extraordinary account of conditions at Dachau, reported that 16.7 per cent of internees returned from that camp after liberation had tuberculosis. An American army officer, A. D. Piatt (4) who served in one of the evacuation hospitals at Dachau, confirmed the high incidence, and called attention to the fulminant character of the disease in liberated inmates of the Camp. Swiss physicians, in several published reports on the health of former camp inmates transferred to Switzerland for care, commented on the high rate of tuberculosis.

There is good reason to believe that the concentration camps served as a focus for the spread of tuberculosis. Immediately after the camps were freed, and until order could be restored through a military organization to control displaced personnel, camp inmates who left the compounds at the time of the liberation wandered almost at will in the surrounding country, looting, and wreaking vengeance on their former captors, seizing food after their long starvation, and often dying in acute gastro-intestinal distress in abandoned buildings after eating to excess. Presumably these wanderers included many tuberculous survivors, with chronic ulcerative forms of the disease, rather than the acute types which were common in those who did not live to effect their escape.

As time went by regroupings occurred and ultimately well defined national aggregations were assembled in the displaced person camps, which are now the subject of great publicity. In the months since the end of the war a steady repatriation has taken place, the tuberculous going with the non-tuberculous, creating an additional burden in the countries to which they returned. Before long another mass migration was under way, as heart rending in its way as the other, although the subject of less sympathy in the place at the time because of the prevailing bitterness, viz., the forced exodus of hundreds of thousands of Germans from Poland and the Sudetenland, to which was added, as a problem for

<sup>2</sup> Personal observation of the writer at the Buchenwald Camp, April 1945.

the hard pressed German public health system, the return of thousands of former prisoners of war to Germany, including many with advanced tuberculosis.

Such was the heritage left by the war in Central Europe. It illustrates the vulnerability of the best laid plans for improvement in national and international public health.

With reduction in military occupation forces in Germany, after some degree of stabilization had occurred and the long awaited demobilization was under way, the task of caring for the camps for displaced personnel was assigned to the United Nations Rehabilitation and Relief Administration. In the health organization of UNRRA certain groups of the Administration were assigned a program for the care and control of tuberculous patients in the camps for displaced personnel. Other divisions of the UNRRA organization had already made a good start toward the control of tuberculosis in ravaged countries which had been liberated some months before the end of the war. The program in Greece was particularly notable (5). As UNRRA teams moved into the various countries an assessment of the incidence of the disease and the total tuberculosis problem was considered of immediate importance.

A review of this early work, well illustrated by graphs and tables, has been given by Marc Daniels (6), a member of the UNRRA staff. With due allowance for the effect of war, with all its destruction, on the tuberculosis control offices in the blighted countries, estimates of some degree of reliability were made on the mortality from tuberculosis in Europe during and after the war. In the mid-war years increases were evident in all the great cities. Daniels quotes recorded rates for Poland, Austria, Czecho-Slovakia, Germany, Italy, France, the Netherlands, Belgium, and England, which illustrate the extent to which tuberculosis rose during the war years. As might be expected, the tuberculosis disaster was greatest in the countries most ravaged. No war time increase occurred in Sweden or Switzerland. In Poland, on the other hand, particularly in devastated cities like Warsaw and Lodz, a rise to three times the old rate occurred. The tuberculosis death rate in Warsaw in 1944 was estimated at 500 per hundred thousand population. Basing his calculations on the increase in deaths in countries where reliable vital statistics were maintained, and using the best estimates possible for the others, Daniels came to the conclusion that the war was responsible for several hundred thousand deaths from tuberculosis in Europe, and that the number of surviving sufferers from the disease must range between five and ten millions, a staggering total for the future program of tuberculosis control.

Another graphic picture with emphasis on the epidemic aspects of the disease, and the high incidence of acute forms has been given by Holm (7). A good review of the rise of tuberculosis in Italy and other parts of Europe has been published by L'Eltore (8), who stressed the high rates in southern and eastern Europe.

The present picture is not wholly dark, however. Remarkable trends toward recovery are already evident. Most countries show a decline in tuberculosis mortality from the peaks reached during the war. The post-war decrease in the death rate from tuberculosis in Warsaw is almost as startling as the rise during the last months of the war. An astonishing reduction in the tuberculosis death

rate has occurred in the Netherlands, a country so ravished by occupation and military operations that on the day of the Nazi surrender only three weeks' food supply remained for the entire country.<sup>3</sup> These remarkable drops from the high peaks of mortality reached in the war seem to have one common explanation. Conditions were so severe that the great majority of tuberculous patients with acute or progressive disease died. The death rate reached a great height during this phase; after it was over, a minority of tuberculous patients were still left to die. In passing, it may be noted that a similar phenomenon occurred during the influenza epidemic of 1918-1919; the curve for the tuberculosis mortality in the United States serves as a good example.

The beginnings of recovery from tuberculosis in the most damaged parts of Europe are highly encouraging. Even at the worst the mortality did not rise to the heights witnessed at the end of World War I, when annual rates in the neighborhood of a thousand per hundred thousand population were recorded in central and southeastern Europe. Even then recovery was rapid, once normal delivery and distribution of food, and restoration of tuberculosis control procedures, were again under way. Progress was interrupted more than once by economic upset, as in Germany in 1921-23, when a fantastic inflation of currency took place, with general loss of savings. It is too early for an accurate evaluation of the progress of recovery in Germany after the second world war, but an orderly restoration of control measures is in progress, and factual reports are becoming available. An unmistakable drop in mortality has occurred after a sharp rise during the war. Great improvement has occurred since 1945 in the reporting of tuberculosis and the provision of beds in the western zones of military occupation. The extent of recovery in eastern Germany is not so clear in available reports. The Berlin sector remains a focus of high prevalence of the disease. The mortality rate, which approached 300 in 1945, has declined since that time, but is still high. There is a gross shortage of beds for tuberculosis in Berlin, but some increase in their number is expected (9).<sup>4</sup>

At the present time a vigorous campaign for improved tuberculosis control is under way in the British Isles, with emphasis on mass X-ray survey and full restoration of sanatorium facilities. The remarkable improvement in the Netherlands, which now has one of the lowest death rates in the world (about 35), has already been mentioned. The severity of the disease during the war was the subject of a report in the first post-war number of the *Bulletin of the International Union against Tuberculosis* (10). The general mortality rate is dropping in the Scandinavian countries, where great stress is laid on extension of prophylactic vaccination by BCG. Denmark in addition to its own national campaign, is

<sup>3</sup> Personal communication to the writer from Dr. H. R. Gerbrandy, chief of tuberculosis control in the Public Health Service in the Netherlands, July 1947.

<sup>4</sup> The report cited was the outgrowth of a survey made at the request of the Public Health Advisor to the British Military Governor in September 1947. It is expected that a report by a commission appointed by the Secretary of the Department of the Army of the United States to make a similar survey in the U. S. Zone of Germany will be released in the near future.

conducting a program of BCG vaccination in eastern and central Europe through the Danish Red Cross (7). Rates below 50 per hundred thousand per annum seem assured in the Scandanavian nations, if unexpected difficulties do not develop.

In central and southern Europe conditions are not so favorable. Indeed in some respects the outlook is not so favorable as in 1920, when tuberculosis rates were far higher than today. Economic conditions in Europe are critical, and full reconstruction cannot proceed until an agreement has been reached in such vital matters as the industrial rehabilitation of Germany and the degree of coordination of effort than can be achieved by representatives of conflicting political systems, which, to say the least, are today in far from perfect accord. Indeed it is not too much to say that the chief difficulties in the way of restoration of public health control, including the control of tuberculosis, are not technical, or even administrative, but political. This fact was all too evident in Greece where "the approval (of a project for tuberculosis control) by a Minister of one government was countermanded by the Minister of the next" (6). Until the necessary security is assured for the construction of an enduring system for public health practice, measures for the control of tuberculosis will lag. If such security does become assured, on the other hand, national programs can thrive again, and organizations of international scope such as the World Health Organization and the International Union Against Tuberculosis, can promote effective long range programs.

ESMOND R. LONG

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Preliminary Program

Joint Annual Meetings

National Tuberculosis Association—44th Annual Meeting

American Trudeau Society—43rd Annual Meeting

National Conference of Tuberculosis Secretaries—26th Annual Meeting

NEW YORK, N. Y.—June 15–18, 1948

*All meetings will be held at the Hotel Pennsylvania*

Saturday, June 12

National Tuberculosis Association

Preliminary Committee Meetings

American Trudeau Society

Preliminary Committee Meetings

National Conference of Tuberculosis Secretaries

Preliminary Committee Meetings

Sunday, June 13

9:30 a.m.

National Tuberculosis Association

Committee Meetings

American Trudeau Society

Council Meeting

National Conference of Tuberculosis Secretaries

Advisory Committee Meetings

2:00 p.m.

National Tuberculosis Association

Committee Meetings

American Trudeau Society

Council Meeting

8:00 p.m.

National Conference of Tuberculosis Secretaries

Executive Committee Meeting

Monday, June 14

9:30 a.m.

**Registration**

**National Tuberculosis Association**

Board of Directors Meeting

**Clinical Programs**

Non-Tuberculous Thoracic Lesions

Bellevue Hospital Chest Service

Lenox Hill Hospital

Advance registration required—See May BULLETIN for further information

2:00 p.m.

**National Tuberculosis Association**

Board of Directors Meeting

**Conference**

Rehabilitation: HOLLAND HUDSON, New York, N. Y., *Chairman*

**Conference**

Nursing: MISS KATHERINE G. AMBERSON, R.N., New York, N.Y., *Chairman*

Tuesday, June 15

9:30 a.m.

**American Trudeau Society**

**Business Session**

HOWARD W. BOSWORTH, M.D., Los Angeles, Calif., *Chairman*

Report of the President—HOWARD W. BOSWORTH, M.D., Los Angeles, Calif.

Report of the Secretary-Treasurer—DAVID A. COOPER, M.D., Philadelphia, Pa.

Reports of Committees

Election of Officers and Council Members

**Clinical Programs**

Non-Tuberculous Thoracic Lesions

Bellevue Hospital Chest Service

Lenox Hill Hospital

Advance registration required—See May BULLETIN for further information

**National Conference of Tuberculosis Secretaries**

**Business Session**

DONALD E. PRATT, St. Louis, Mo., *Chairman*

Report of the President—DONALD E. PRATT, St. Louis, Mo.

Report of the Secretary-Treasurer—FRANK W. WEBSTER, Raleigh, N.C.  
 Reports of Advisory Committees  
 Reports of Special and Joint Committees

2:00 p.m.

## Medical and Public Health Sections

### Joint Session

ROBERT J. ANDERSON, M.D., Washington, D. C., *Chairman*

#### Community Surveys and Follow-Up

*A Report on the Minneapolis Survey*—F. J. HILL, M.D., M.P.H., Minneapolis, Minn.

*A Report on the Sacramento Survey*—LAURENCE R. KIRK, San Francisco, Calif.

*A Report on the Florida Surveys*—C. M. SHARP, M.D., Jacksonville, Fla.

*The Responsibility of Organized Medicine and the Private Physicians in Mass Surveys*—ARTHUR C. CHRISTIE, M.D., Washington, D.C.

*The Tuberculosis Association and Its Contribution to Communitywide Surveys*  
 —MISS MARIAN S. NEVERS, Quincy, Mass.

*Follow-Up—Its Magnitude and Importance*—PAUL S. PHELPS, M.D., Hartford, Conn.

8:00 p.m.

## General Meeting

Report of the Committee on Nominations

Introduction of Guests

Award of the Trudeau Medal

Address of the President

Report of the Executive Office

Wednesday, June 16

8:15 a.m.

## Medical Section

### Seminar

H. McLEOD RIGGINS, M.D., New York, N.Y., *Chairman*  
 Streptomycin

#### Participants:

EDWARD N. PACKARD, M.D., Saranac Lake, N.Y.

WILLIAM STEENKEN, Saranac Lake, N.Y.

JOHN W. STREIDER, M.D., Boston, Mass.

KIRBY S. HOWLETT, JR., M.D., Shelton, Conn.

GUY P. YOUNG, M.D., Cleveland, Ohio

SIDNEY J. SHIPMAN, M.D., San Francisco, Calif.

CORTIS MCCAY FLORY, M.D., New York, N.Y.

CARL MUSCHENHEIM, M.D., New York, N.Y.

10:00 a.m.

**Medical Section**ESMOND R. LONG, M.D., Philadelphia, Pa., *Chairman*

Chemotherapeutics and Antibiotics

*Antibiotics as Chemotherapeutic Agents*—SELMAN A. WAKSMAN, Ph.D., New Brunswick, N. J.*Streptomycin in Genito-Urinary Tuberculosis*—WILLIAM H. STEARNS, M.D.; JOHN K. LATTIMER, M.D.; JOSEPH W. SCHWARTZ, M.D.; J. BURNS AMBERSON, M.D., New York, N.Y.*Otic Toxicity of Streptomycin*—EDMUND P. FOWLER, JR., M.D., New York, N.Y.  
*The Effect of Streptomycin, Para-amino-Salicylic Acid and Their Combination on the Tubercle Bacillus in vitro and on Experimental Tuberculosis*—ROBERT G. BLOCH, M.D.; ROBERT H. EBERT, M.D.; KIRSTEN VENNESLAND, M.D., Chicago, Ill.

Discussors:

GEORGE E. MARTIN, M.D., Pittsburgh, Pa.

H. J. CORPER, M.D., Denver, Colo.

F. MAURICE MCPHEDRAN, M.D., Philadelphia, Pa.

JOHN B. BARNWELL, M.D., Washington, D.C.

9:30 a.m.

**Public Health Section**EZRA BRIDGE, M.D., Rochester, N.Y., *Chairman*

Responsibilities after Case-Finding

*From the Standpoint of the Tuberculosis Controller*—JOSEPH B. STOCKLEN, M.D., Cleveland, Ohio

Discussion Groups:

*Voluntary Tuberculosis Association*—MURRAY A. AUERBACH, Indianapolis, Ind., *Leader**Supplementary Services—Social Welfare and Casework; Rehabilitation; Occupational Therapy; Public Health Nursing*—HAROLD MCGEE, Richmond, Va., *Leader**Health Department—Case Registers; Follow-Up in Home; Clinics; Nursing Services*—JOSEPH I. LINDE, M.D., New Haven, Conn., *Leader**Direct Medical Services—Hospital; Clinic; Private Physician; Nursing*—H. J. NIMITZ, M.D., Cincinnati, Ohio, *Leader*

Summary—Discussion Leaders

2:00 p.m.

**Medical Section**HERBERT C. MAIER, M.D., New York, N.Y., *Chairman*

Surgery—Trends—Late Results

*Late Non-Tuberculous Complications of Tuberculosis Hilar Lymphadenitis*—JEROME R. HEAD, M.D., Chicago, Ill.*Late Results of Thoracoplasty Analyzed According to Type of Lesion*—THOMAS J. KINSELLA, M.D.; E. S. MARRIETTE, M.D.; P. M. MATTILL, M.D.; E. P. K. FENGER, M.D.; V. K. FUNK, M.D.; L. M. LARSON, M.D.; S. S. COHEN, M.D.; F. C. NEMEC, R. R. L., Minneapolis, Minn.



*Early Closed Intrapleural Pneumonolysis in the Treatment of Tuberculosis*—OTTO C. BRANTIGAN, M.D., Baltimore, Md.

*Decortication of the Lung in Patients with Pulmonary Tuberculosis*—P. V. O'ROURKE, M.D.; E. J. O'BRIEN, M.D.; W. M. TUTTLE, M.D., Detroit, Mich.

*Pulmonary Resection in the Treatment of Tuberculosis*—JOSEPH W. GALE, M.D.; HELEN A. DICKIE, M.D.; ANTHONY R. CURRERI, M.D., Madison, Wis.

Discussor:

JOHN B. GROW, M.D., Denver, Colo.

## Public Health Section

H. STUART WILLIS, M.D., McCain, N.C., *Chairman*

Hospital Facilities for the Tuberculous

*Quantity and Quality of Tuberculosis Beds in the United States Today*—MYRON D. MILLER, M.D., Washington, D.C.

*Standards for Tuberculosis Hospital Beds*—F. H. ARESTAD, M.D., Chicago, Ill.

*Methods Used to Improve Hospital Facilities in:*

*Colorado*—ROY CLEERE, M.D., Denver, Colo.

*New York State*—ROBERT E. PLUNKETT, M.D., Albany, N.Y.

*Veterans Hospitals*—J. N. WILSON, M.D., Rutland Heights, Mass.

*Implications to:*

*The Tuberculosis Association*—MISS PANSY NICHOLS, Austin, Texas

*Government*—ARTHUR W. FISKE, Cleveland, Ohio

8:00 p.m.

## Medical Section

Clinico-Pathological Conference

J. BURNS AMBERSON, M.D., New York, N.Y., *Chairman*

Participants:

RALPH ADAMS, M.D., Louisville, Ky.

MARCY SUSSMAN, M.D., New York, N.Y.

DONALD S. KING, M.D., Boston, Mass.

## National Conference of Tuberculosis Secretaries

Executive Committee Meeting

Thursday, June 17

9:30 a.m.

## Medical Section

Chairman to be announced

After-Care

*Rehabilitation of Tuberculous Patients in a Large Institution*—JOSEPH B. STOCKLEN, M.D., Cleveland, Ohio

*Employment of Tuberculous Ex-Patients in Industry*—HENRY S. HAMMOND, Washington, D.C.

*Rehabilitation of Tuberculous Veterans*—B. B. BAGBY, JR., M.D., Oteen, N.C.

*Summary of Present Status of Medical Rehabilitation*—NORVIN C. KIEFER, M.D., Washington, D.C.

## Public Health Section

REGINALD ATWATER, M.D., New York, N.Y., *Chairman*

Improvement of Tuberculosis Control through Local Health Units

- Development of Local Health Units*—HAVEN EMERSON, M.D., New York, N.Y.  
*The Role of the Tuberculosis Association in the Development of Local Health Units*  
 —JAMES G. STONE, New York, N.Y.  
*Experience in Local Health Units in the State of Illinois*—RICHARD F. BOYD,  
 M.D.; CHARLES F. SUTTON, M.D., Springfield, Ill.  
*Developing a District Tuberculosis Association*—MRS. ROBERT S. HICKEY, New-  
 port, Tenn.

2:00 p.m.

## Medical Section

H. STUART WILLIS, M.D., McCain, N.C., *Chairman*

## Research and Therapy

- Chemical and Immunological Investigations on the Tubercle Bacillus and Serum*—  
 DENNIS W. WATSON, M.D.; ROBERT J. HECKLY, M.D., Madison, Wis.  
*Prognosis of Primary Tuberculosis in Children*—EDITH M. LINCOLN, M.D.,  
 New York, N.Y.  
*Primary and Reinfection Type Tuberculosis in Young Adults: Five to Fifteen Year  
 Follow-Up*—THEODORE L. BADGER, M.D., Boston, Mass.  
*X-ray Findings among Student Nurses on Admission to Training*—CARROLL E.  
 PALMER, M.D.; LYDIA EDWARDS, M.D., Washington, D.C.  
*Definition of What Constitutes Positive Sputum:*  
*From Laboratory Point of View*—C. EUGENE WOODRUFF, M.D., Northville,  
 Mich.  
*From Clinical Point of View*—HOWARD W. BOSWORTH, M.D., Los Angeles,  
 Calif.

## Public Health Section

FRANK W. WEBSTER, Raleigh, N.C., *Chairman*

## Community Organization for Health Education

- Fundamental Concepts in Community Organization for Health Education*—MISS  
 MURIEL F. BLISS, Hartford, Conn.  
*Evaluating Our Progress*—MISS FRANCES L. KRAFT, New York, N.Y.

## Discussion Groups:

- Developing Public Participation*—MISS A. HELEN MARTIKAINEN, Raleigh, N.C.,  
*Leader*  
*Developing Participation of Special Groups*—ALFRED E. KESSLER, Indianapolis,  
 Ind., *Leader*  
*Board of Education Leading to Community Organization*—MRS. HAROLD K. MOSLE,  
 Santa Paula, Calif., *Leader*  
*Developing School Participation*—MISS CLAUDIA B. GALMER, Bethesda, Md.,  
*Leader*

## Summary—Discussion Leaders

Friday, June 18

8:15 a.m.

## Medical Section

## Seminar

- DICKINSON W. RICHARDS, M.D., New York, N.Y., *Chairman*  
 Cardiac Dysfunction in Chronic Pulmonary Disease

## Participants:

DICKINSON W. RICHARDS, M.D.

DAVID SPAIN, M.D.

ANDRÉ COURNAND, M.D., New York, N.Y.

9:30 a.m.

**Medical and Public Health Sections**

## Joint Session

HERMAN E. HILLEBOE, M.D., Albany, N.Y., *Chairman*

Some Unmet Needs in Tuberculosis Control—A Challenge for the Future

*Clinical and Chemotherapeutic Measures in Tuberculosis*—P. D'ARCY HART,  
M.D., London, England*Possibilities and Limitations of Antibacterial Drug Therapy in Tuberculosis*—

H. CORWIN HINSHAW, M.D., Rochester, Minn.

*Unmet Needs in Tuberculosis Control*—W. P. SHEPARD, M.D., San Francisco, Calif.

12:30 p.m.

**General Meeting**Brief talks by the incoming presidents of the National Tuberculosis Association,  
American Trudeau Society and National Conference of Tuberculosis Secretaries

1:00 p.m.

**Joint Luncheon**Executive Committees of the National Tuberculosis Association, American Trudeau  
Society and National Conference of Tuberculosis Secretaries

2:30 p.m.

**American Trudeau Society**

## Council Meeting

**Clinical Programs at Various New York Hospitals**

Hospitals to be announced

Advance registration required—See May BULLETIN for further information

**Adjournment**

## *AMERICAN TRUDEAU SOCIETY*

### Streptomycin Panel Discussion at Annual Meeting in New York

At the Annual Meeting to be held in New York June 15 to 18, 1948, Dr. H. McLeod Riggins will serve as Chairman of a panel for the discussion of the use of streptomycin in tuberculosis. He hopes to keep this discussion as informal as possible and requests that the members of the American Trudeau Society please send him, at the following address, any questions on streptomycin which they wish to have discussed—140 East 54th Street, New York 22, New York.



# THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

VOLUME LVII

APRIL, 1948

ABST. No. 4

**Children's Tuberculosis Clinic.**—In Newcastle-upon-Tyne, where there was always a high tuberculosis mortality, a clinic was established for children under 5 years of age who had contact with tuberculosis. The object was to obtain information concerning mortality and morbidity of tuberculosis in children from families containing a notified case of the disease, and to ascertain the relation which this bears to the total mortality and morbidity for the same age group within the city. The clinic resembles closely the diagnostic clinic for childhood tuberculosis suggested in the British Paediatric Association Report in 1943. The present report covers the period from June, 1941 to December, 1945. The work is carried on in a special clinic established in the children's department in Newcastle-upon-Tyne General Hospital. Parents are more willing to bring young children to such a clinic than to a tuberculosis dispensary. All contact children are tuberculin-tested and X-rayed. Tram or bus fares are paid when this seems necessary in order to get the children to the clinic. Only about 10 per cent of the notified patients have failed to report for examination. For a more detailed working plan, one is referred to the original article. From June, 1941 to December, 1945, 569 children were listed, of whom 520 were examined at least once. Half of the children in contact with "open" tuberculosis were positive, and one-fifth of those in contact with "closed" pulmonary cases were positive at the first examination. Thirty-five subsequently converted. Of the 142 positive reactors at the first examination, 110 were contacts of known sputum-positive cases, and 32 were contacts of negative cases.

Of 227 negative reactors, 103 were contacts of sputum-positive cases, and 124 of sputum-negative cases. The author believes that nothing can be done in hospitals for children with symptomless primary tuberculosis which cannot be done in a good home. The only reasons for admission to a hospital are unfavorable home conditions or the absence of any good method of separation from infection. Of the 369 children who had been in contact with pulmonary tuberculosis, 57 were admitted to hospitals because of symptoms or for other good reasons. An additional 8 were admitted with acute disseminated tuberculosis or tuberculous meningitis. The mortality of this same group of 369 children exposed to pulmonary tuberculosis has been 5 per cent up to the end of 1945; this figure is high enough to make use of the word "benign" in connection with childhood tuberculosis a very dangerous one. Thus in 320 families containing an adult with pulmonary tuberculosis, there were at least 21 deaths of young children during a period of four and one-half years. The risk of exposure is greatest in the first year, and there is a marked decrease after the age of 2. Examination of 19 children who died showed that 9 had been tuberculin-negative at the first examination, and 8 of these were under 2 years of age. It was estimated that the provision of sufficient beds during a four and one-half year period would cost, apart from establishment and capital charges, approximately 4,000 pounds a year. The foster-parent scheme would cost approximately 3,000 pounds a year, but it would be difficult to obtain enough suitable foster parents. The institution might also be used while BCG was being given to tuberculin-

negative children, their stay being limited to the period of development of sensitivity.—*Work of a Tuberculosis Contact Clinic for Young Children, 1941-5, F. J. W. Miller, Brit. M. J., July 19, 1947, 4515: 91.*—(R. W. Clarke)

**Bovine Tuberculosis in Argentina.**—In order to determine the prevalence of human tuberculosis of bovine origin in Argentina, 226 specimens from different places were examined. The bovine type of the tubercle bacillus was identified 13 times (5.75 per cent) and an intermediate type 27 times (11.9 per cent). In 5 of the 13 patients nonpulmonary tuberculosis and in the other 8 pulmonary tuberculosis was present. The presence of intermediate forms is probably significant, as most workers assign a bovine origin to this type. (Bovine tuberculosis was first identified in Argentina by Lignieres in 1904 in one of 6 children with intestinal tuberculosis and fed with cow's milk.)—*La tuberculosis humana de origen bovino en la Argentina, A. R. Arena & A. Cetrángolo An. Cáted. de pat. y clín. tuberc., June, 1946, 8: 86.*—(A. A. Moll)

**Tuberculosis in Brazil.**—In 6 of the 14 state capital cities in Brazil, tuberculosis ranks as the leading cause of death, in 6 others it occupies the second place, and in 2 the third place. Taking the 14 cities together, tuberculosis claims top place. It also leads in the North, Eastern and Southern areas of the country, and is exceeded only by infantile diarrhea and enteritis in the Northeastern area and barely outclassed by heart disease in the Central West region. In the Federal District (Rio de Janeiro), tuberculosis, with 19,295 deaths and 18.6 per cent of the general death rate, had first place in the 1943-1945 three-year period, exceeding heart disease, which is credited with 16,545 deaths and 16 per cent of the general death rate during the same span of time.—*A Tuberculose como causa de morte em algumas capitais Brasileiras, R. de Paula Souza, A. Galdino & R. Albuquerque, Rev. brasil. de tuberc., March-April, 1947, 16: 99.*—(A. A. Moll)

**Primary Tuberculosis in a Slum District.**—Among children in a slum district in one of the Rio de Janeiro beaches, superinfection due to overcrowding and promiscuity became the most important factor in the development and spread of severe types of primary tuberculosis. A roentgenographic survey disclosed, among 897 infants and children, 65 cases (7.2 per cent) of tuberculosis, as compared to 11 cases (3.2 per cent) among 327 children in an adjoining, but much more hygienic, housing project. Primary cases were found even among infants and their proportion reached 13.8 per cent among children one to 6 years old in the slum, as compared to 5.1 per cent in children of the same age in the housing project. While discrete types prevailed among the latter children, the rate decreased to 29.2 per cent in the slum group, the rest being severe types of the disease. The size of the problem may be gathered from the fact that about 400,000 persons live at Rio under such slum conditions.—*Formas de tuberculose de primo-infecção encontradas em crianças de uma favela do Rio de Janeiro, R. de Paula Souza, E. Arruda do Nascimento & A. Cerqueira Alvim, Rev. brasil. de tuberc., March-April, 1947, 16: 117.*—(A. A. Moll)

**Nonpulmonary Tuberculosis in Mexico.**—Although admittedly incomplete, the data on nonpulmonary, and incidentally also pulmonary, tuberculosis in Mexico reflect accurately the changes in the tuberculosis situation. During the last twenty-five years the rate of nonpulmonary tuberculosis has decreased about twice as much as the general tuberculosis and the pulmonary tuberculosis rates. While the latter have revealed but little change in their ups and downs, the death rate for nonpulmonary tuberculosis has moved more violently and in opposite direction to the other two. It increased in the 1930-1939 period and has decreased since. The decrease, however, is not general or uniform, as the nonpulmonary tuberculosis death rate is increasing in women—perhaps due to a greater participation in industry—and also in the 5-9 year and 10-14 year age groups. Probably

because of improved diagnostic methods, there is also an apparent increase in such types of nonpulmonary tuberculosis as affect the spine, the peripheral lymph nodes and the urogenital system. Death rate for tuberculosis of all types in Mexico in 1944 averaged 50 per 100,000 and for nonpulmonary tuberculosis about 5 per 100,000. Figures for 1945 were even lower. The so-called Northern and the Yucatan areas are still having high nonpulmonary tuberculosis death rates (above 10 per cent of the total tuberculosis death rate). The North and Central Pacific regions come next and the South Pacific areas, especially Chiapas and Oaxaca, last of all (less than 5 per cent). Altogether, 9 of the 33 States and Territories still have nonpulmonary tuberculosis death rates exceeding 10 per cent of the total tuberculosis rate. Most prevalent nonpulmonary types are alimentary (2.38 per 100,000), meningeal (91.2), miliary (0.66) and Pott's disease and lymph node tuberculosis (about 0.4 each). In 1944, rates in women were higher than in men in the age groups 15-39 years and 60 and over. Mexico is now apparently in the arrested nonprogressive detubercularization phase of the disease, calling for a more intensive effort to prevent epidemic flare-ups.—*Mortalidad por tuberculosis extrapulmonar en la República Mexicana, I. Cosío Villegas & C. Díez Fernández, Rev. mex. de tuberc., July, 1947, 8: 281.*—(A. A. Moll)

**Tuberculosis in Uruguay.**—Tuberculosis deaths in Uruguay in 1944 totaled 2,470 (110.5 per 100,000), 2,176 (94.5 per 100,000) belonging in the pulmonary group. Tuberculosis is causing 12.4 per cent of the general mortality, being exceeded only by heart disease and cancer as a cause of death. The proportion of deaths among men from tuberculosis is 54.2 per cent, and the male sex leads at all age groups with the exception of the 15-29 year group (in which the tuberculosis death rate is 50 per cent larger for women) and the 0-14 year group (in which the rate is equal for both sexes). Uruguay has 3,000 beds for tuberculous patients and construction under way will raise the total to 5,000, that is, 2 beds per

death. This will place Uruguay ahead of all other countries in Latin America. Other adverse factors remain uncontrolled. One-eighth of the population (over 250,000 persons) still live in unhealthful dwellings; wages are still inadequate in many cases; social security measures have been barely attempted. Mass surveys should be extended and BCG used on a larger scale. Klebanov's recent account of its success in Russia shows better than any previous report what tuberculosis vaccination can accomplish.—*Consideraciones sobre la lucha antituberculosa actual, P. Purriel & A. A. Piaggio, Hoja fisiol., June, 1947, 7: 74.*—(A. A. Moll)

**Tuberculosis Epidemic.**—Three years of observation following an epidemic outbreak of tuberculosis in a state school for young girls in Denmark have indicated that the tuberculin-negative group was the most seriously affected. Three hundred sixty-eight pupils between 12 and 18 years of age were exposed to a teacher whose apex was found to contain a cavity and whose sputum was occasionally positive during the course of an upper respiratory infection. Of the 94 tuberculin-negative girls who were exposed to the infection, 70 became positive reactors. Thirty-seven (58.6 per cent) of these showed the presence of tubercle bacilli in gastric lavage specimens and 36 showed definite pathological roentgenological changes in chest films. Progressive pulmonary tuberculosis subsequently developed in 6 of these invertors, one of whom died; the others received pneumothorax treatment. Other evidences of primary infection were erythema nodosum in 8 cases, pleurisy (three to eleven months after the infection) in 10 cases, pericarditis in one case and peritonitis in one case. The primary infiltrations were found chiefly in the infraclavicular region and in the middle lung field, appearing about three months after the infection. Among the 106 BCG-vaccinated pupils who were exposed to the infection, 2 cases of pulmonary tuberculosis appeared about one year after the exposure. One hundred and five tuberculin-positive girls were exposed, of whom 4 de-



veloped clinical disease with positive gastric lavage, although 2 of these girls may have suffered an endogenous reinfection rather than a superimposed infection.—*Epidemic of Tuberculosis in a State School, T. V. Hyge, Acta tuberc. Scandinav., 1947, 21: 1.*—(P. Q. Edwards)

**Tuberculosis Epidemic.**—A 20-year-old maid-servant with active tuberculosis was responsible for an epidemic of the disease in two different communities in the Faroe Islands. The first group of cases occurred in the hotel where she was employed for five months. Twenty-seven people with whom she had contact were examined. Twelve tuberculin-positive persons showed no evidence of disease while of 15 tuberculin-negative contacts, only 2 stayed negative. The 13 converters (changed from negative to positive on tuberculin test) were the people in whom active disease was found: 4 had initial fever only, 2 had initial fever and pleuritis and 3 had pleuritis only. When this girl was found to be ill, she was sent to a hospital where the diagnosis of active tuberculosis with positive sputum was made. Within two weeks she was transferred to a sanatorium, although during that brief period of time 9 cases of tuberculosis were contracted to be discovered within the next several months. All 9 of these cases had been tuberculin-negative prior to their association with the girl. All converted and several different types of disease were manifested as the primary infection: initial fever, 4; initial fever and pleuritis, 2; initial fever and meningitis, 2 (both died); initial fever and pleuritis and meningitis, 1 (died). BCG is now being given to all people with negative tuberculin reactions, since about 50 per cent of the adults on Faroe Islands are negative reactors.—*A Tuberculosis Epidemic on the Faroe Islands, A. Poulsen, Acta tuberc. Scandinav., 1947, 21: 58.*—(P. Q. Edwards)

**Tuberculosis in Unexpected Deaths.**—In 1,332 postmortem examinations from the Medical Examiner's Office of Manhattan (1,038 white persons and 294 Negroes), tuberculous cavities were found in the lungs of 61

(4.58 per cent). In only 6 of these had the diagnosis of tuberculosis been made clinically. In Negroes there was little difference in relation to sex; in white persons tuberculous cavities were 7.7 times more frequent in males than in females. Forty-nine of the 61 persons with cavities were white males, 45 of whom were over 40 years of age. In 87 per cent of the cases the cavities were in the upper lobes. Sixteen persons (between 22 and 68 years of age) presented progressive primary tuberculosis; 27 persons (between 33 and 76 years of age) had healed primary infection and progressive new disease; in 18 patients there was progressive disease of an indeterminate nature.—*Incidence of Tuberculous Pulmonary Cavities in Unexpected Deaths Investigated at Necropsy, E. M. Medlar, Arch. Int. Med., September, 1947, 80: 407.*—(G. C. Leiner)

**Positive Gastric Lavage and Infectiousness.**—Because there is still considerable difference of opinion in academic circles about the actual infectiousness of gastric-lavage-positive people, a study was undertaken in Sweden to ascertain exactly how many new tuberculin-positives can be traced to a gastric-positive person. Environment groups were used for this study, family, contact and work-place environments being included for each of three series: gastric-negatives, gastric-positives and sputum positives. Results clearly show a significantly higher incidence of contact infection in the sputum-positive environment than in the other two. No significant difference was found in the contacts with the gastric-positive and gastric-negative groups. Gastric-lavage-positives are thus shown to be non-infectious. These investigations further show that there is no difference in the risk of infection from gastric-lavage-positives if the source of infection is a primary or a post-primary, or if the carrier is a child or an adult. Warning is given to be sure that every gastric-positive case is not likewise sputum-positive before informing him of his non-infectiousness.—*Is There Any Risk of Infection from Gastric-lavage Positive? L. Bluhm, Acta tuberc. Scandinav., 1947, 21: 70.*—(P. Q. Edwards)

# PNEUMOPERITONEUM IN THE TREATMENT OF PULMONARY TUBERCULOSIS<sup>1</sup>

407 Consecutive Cases

HAROLD GUYON TRIMBLE,<sup>2</sup> J. LLOYD EATON,<sup>2</sup> GERALD L. CRENSHAW<sup>2</sup> AND  
INA GOURLEY<sup>2</sup>

The introduction of air into the abdominal cavity by means of needle puncture is an old procedure. It has been used for the local treatment of tuberculous peritonitis since 1893 (1).

Banyai's (2) article in 1934, in which he discussed nine cases of pulmonary tuberculosis treated by the combined use of phrenic nerve operation and pneumoperitoneum when pneumothorax was found to be impossible, seemed reasonable to us. We, like many others, had observed that some women with pulmonary tuberculosis tended to become worse during the year following childbirth, but that during the course of pregnancy, itself, active pulmonary tuberculosis frequently showed a marked improvement. An often discussed question among us was whether this improvement during pregnancy, with the subsequent tendency for breakdown after delivery, was due to the change in the position of the diaphragm, obvious during this period by X-ray or fluoroscopic observation, or, whether it was due to some hormonal change. Banyai's article suggested that it was the mechanical effect of the rise of the diaphragm which was beneficial, and pneumoperitoneum provided a method of reproducing the mechanical effects of pregnancy in tuberculous women, besides also being applicable to males. As, prior to 1934, we had occasionally used oxyperitoneum for the symptomatic relief of tuberculous peritonitis, we were acquainted with the technique, and started using the procedure. Its effectiveness, the relative lack of complications as compared with pneumothorax collapse, and autopsy examination (3) which failed to show serious reactions in the peritoneum or abdominal organs, encouraged us to continue.

The present paper is a study of 407 consecutive patients who have been treated by us during all, or most of their treatment. It does not include the cases reviewed in 1937 (4), as they were patients in our County Hospital System. We felt it better to analyze a group of patients in which we could have good follow-up, and in which treatment had been adequately used according to our lights, and in which results could therefore be more accurately evaluated.

With the recent appearance of Banyai's book (5), which is an exhaustive study up to 1946 of all the literature on pneumoperitoneum, it is unnecessary to review at any length many of the subjects considered there. However, because pneumoperitoneum therapy has been used only for a period of years (as contrasted with pneumothorax which has been in use for decades) no long-time results have appeared in the literature. The present paper is a presentation of

<sup>1</sup> This study was made possible in part by the Philip Pierson Memorial Research Fund of Alum Rock Sanatorium, San Jose, California.

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CASE 1. J. A., white, female aet. 40 years. Past history of dry cough for 6 weeks and hemoptysis 4-13-40. X-ray 4-15-40 showed minimal exudative pulmonary tuberculosis left apex. Sputum positive. Another hemoptysis 4-17-47 with acute spread throughout

our results to date. We would like to emphasize the fact that the purpose of pneumoperitoneum in our opinion is a mechanical one:—we attempt to obtain a rise of the diaphragm thus reducing the pulmonary volume (see X-ray illustrations). Banyai (5) takes up the question of the reduction of pulmonary volume at some length, and although some of the earlier work (6) dealing with the effect of phrenic evulsion is not in agreement, there seems to be little doubt that a mechanical rise of the diaphragm reduces the total pulmonary volume. The studies of Pai and Rao (7) with phrenic exairesis, and our own serial X-rays of patients with adequate pneumoperitoneum add additional proof. (We can demonstrate a beneficial effect within a period of weeks on tuberculous lesions in a majority of our cases, whether the lesions are apical or basal.) It should be remembered that in certain instances, disease conditions, particularly those of pleural adhesions with diaphragmatic fixation, may alter and at times markedly limit the rise of the diaphragm and its effect on the lung volume. In such cases, even where the diaphragm of one hemithorax is relatively fixed, the rise of the diaphragm on the opposite side, with ipsilateral shift of the heart and mediastinum, may cause a beneficial partial collapse of the diseased lung.

With this rise in the diaphragm and the accompanying reduction of pulmonary volume, we get another effect from an adequate pneumoperitoneum. At this higher level, the diaphragm is limited in motion, as is readily seen by fluoroscopic observation. When the diaphragm is thus observed during ordinary respiration, it functions at a higher level than previously, and its motion is definitely limited. True, on deep inspiration it can achieve a stroke practically the same as though pneumoperitoneum were not present, and an ordinary X-ray film taken on deep inspiration may not show much change in its position. With quiet breathing, however, fluoroscopically observed, the extent of the diaphragmatic excursion shows very definite limitation.

On a theoretical basis and without wide practical experience, many physicians seem to consider the initial introduction of air into the abdominal cavity a hazardous procedure. Prior to the therapeutic use of pneumoperitoneum in pulmonary tuberculosis, the introduction of air into the abdominal cavity probably received widest use in connection with peritoneoscopy in evaluating abdominal

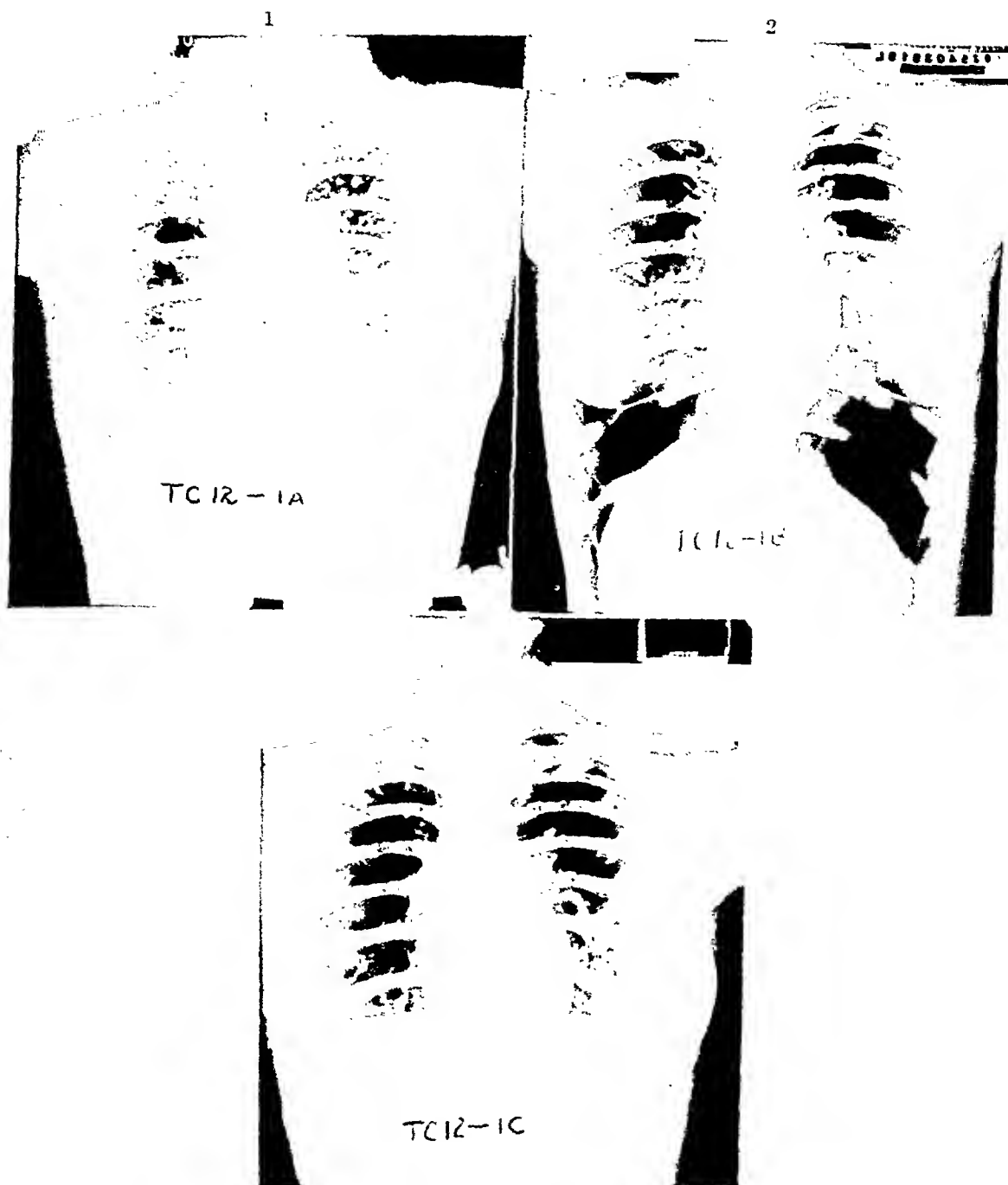
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the left lung and into right mid-lung field. On 4-18-40, an ineffective left pneumothorax was initiated.

#1. X-ray 4-25-40 shows pulmonary tuberculosis 3C, with acute exudative pulmonary tuberculosis throughout the left lung and in the right mid-lung field. There is an ineffective pneumothorax left. Left pneumothorax abandoned. Left phrenic crush 5-1-40. Pneumoperitoneum initiated 5-4-40.

#2. X-ray 7-22-40 shows marked improvement; adequate pneumoperitoneum with marked rise of left diaphragm from pneumoperitoneum plus phrenic. Sputum negative since July 1940. Began graduated work-up 10-1-40. Pneumoperitoneum continued to 8-27-44, a period of 51 months.

#3. X-ray 2-1-47 (2½ years after pneumoperitoneum discontinued) shows almost complete clearing of previous infiltrations—some fibrosis remaining left apex. Left diaphragm remains elevated and function limited from phrenic nerve operation. Normal working efficiency for 6 years.



CASE 2. P. S., white, female aet. 26 years. Past history of pleurisy with effusion, right, in 1930. October 1937 prolonged respiratory symptoms, hoarseness for 4 months, persistent cough. January 1939 persistent cold, loss of weight, sputum positive.

1. X-ray 4-9-39 shows a 5 cm. cavity right upper lobe with acute exulative spread throughout both lungs. Right pneumothorax attempted, no free pleural space. Pneumo-

disease. Ruddock (8) in more than 1000 such examinations amply demonstrated the safety of the procedure. Narancio, et al. (9), refer to peritoneoscopy as "this relatively safe minor procedure". Kelling (10) maintains in his early writing on the subject that the mobility of the intestines in the living subject is such that they will not sustain injury but will recede or slip aside before the gentle and slow thrust of the trocar. This same has been brought out by Jacobaeus (11), and Ruddock (12), and other writers on peritoneoscopy. Ruddock (12) is of the opinion that any viscus unless so adherent that all freedom of movement is gone, will slip aside before the thrust of the trocar in the living subject. The intestine may be punctured by this method should it be firmly attached to the parietal peritoneum by adhesions. Puncture of the bowel occurred in his series of 500 cases eight times. Each time the instrument was left in place and an abdominal incision made. In each instance, the trocar could have been removed without soiling the peritoneal cavity, as the bowel was firmly plastered against the parietal peritoneum.

The fear of bowel puncture seems to be the deterring influence in the minds of many physicians who consider starting the use of a therapeutic pneumoperitoneum on their own tuberculous patients. Our own experience, as that of the authors cited above, amply demonstrates the relative safety of its induction.

A few points in general and in regard to technique may not be amiss. For initial induction, we prefer a point slightly to the left and below the umbilicus, or in the left upper quadrant just below the rib cage. A history of previous abdominal surgery, even though extensive, such as the removal of a gall bladder, bowel resection or gynecological surgery is not a contraindication to the attempted induction of pneumoperitoneum. Even in such instances, it is very seldom that a mechanically satisfactory pneumoperitoneum cannot be induced.

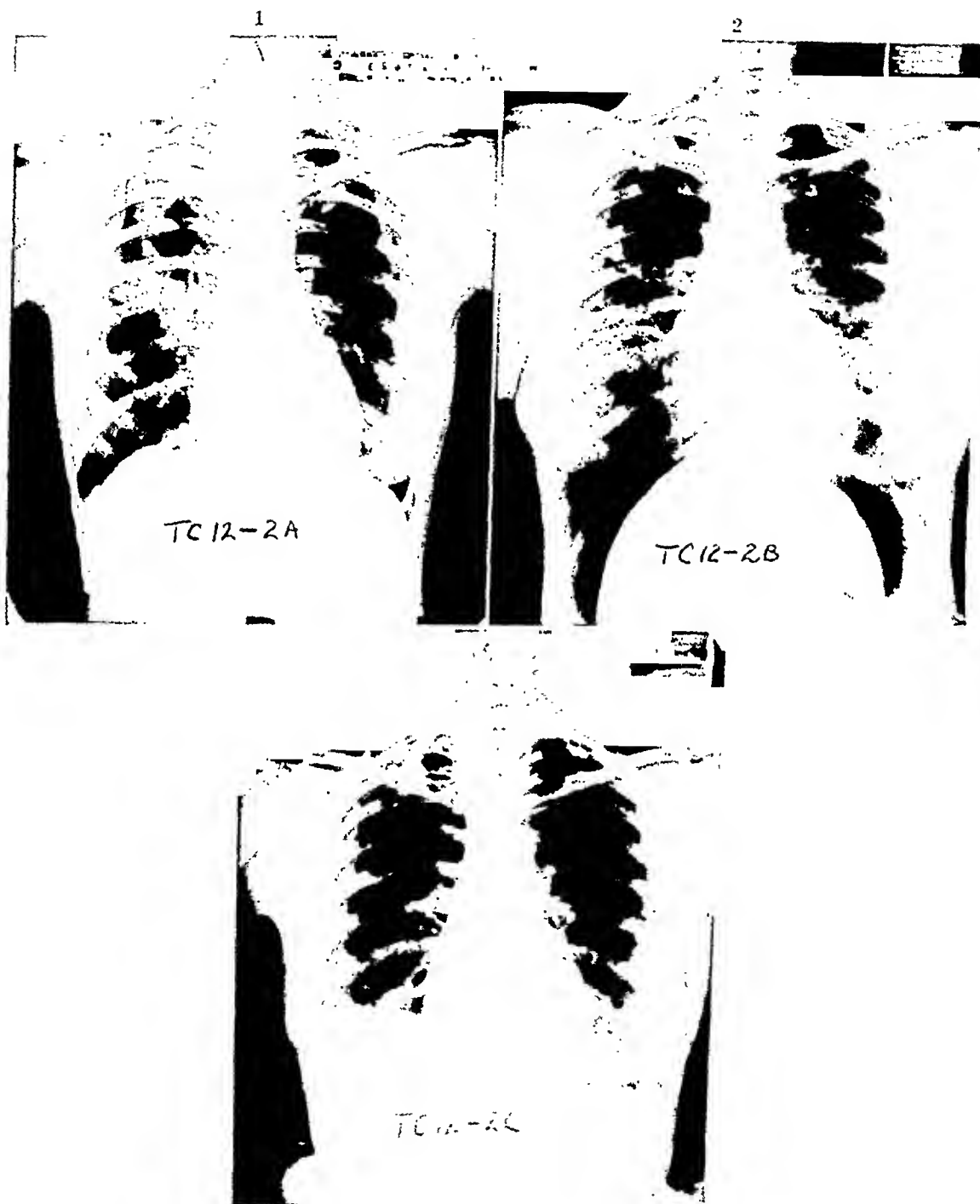
For pneumoperitoneum refills, we find that the manometric readings are of but little value except to indicate that the needle is in the peritoneal space. Tension or relaxation on the part of the patient, the character of the musculature, and various other factors influence these readings markedly. Contrast this to pneumothorax where the manometric readings are of fundamental significance. Certainly in pneumoperitoneum the manometer is not the guide as to the amount of air per refill or to the frequency of refills. This can be decided only by fluoroscopic control, noting whether the rise of the diaphragm is adequate, and keeping an amount of air in the peritoneal cavity sufficient to maintain this rise. We have seen others administering pneumoperitoneum inadequately, with insufficient air per refill and at intervals too far apart to achieve and maintain the objective

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peritoneum induced 4-13-39. Cavity closed, sputum negative. Patient ambulatory within 6 months; returned to full-time work in 14 months.

#2. X-ray 10-24-40 shows adequate rise of diaphragm from pneumoperitoneum without phrenic. Few fibrotic strands throughout both lungs representing previous exudative lesions. Fibrotic scar 1st interspace right, remains of previous cavity. Pneumoperitoneum allowed to absorb and lung completely expanded by July 27, 1944, after 5 years of pneumoperitoneum collapse.

#3. X-ray 8-3-44 and fluoroscopic examinations to date show same findings. Normal pregnancy completed 2-11-46. Last follow-up 3-31-47; patient completely well.



CASE 3. M.S., white, female, act. 52y. cts. Past history of more or less productive cough since February 1933; increase in weakness, cough and sputum since December 1938, hemoptysis 2-13-39.

81. X-ray 2-14-39 shows fibrotic tuberculosis right upper lobe with a 3½ cm. cavity in

of an adequate rise of the diaphragm. Our average maintenance refill is between 800-1000 cc. of air at weekly intervals. It is seldom that a patient can go ten days between refills, and practically never two weeks and still keep the kind of pulmonary collapse we find effective.

We usually maintain pneumoperitoneum for at least four, or preferably five, years. A pneumoperitoneum that has been abandoned voluntarily can be re-induced, in contrast to pneumothorax where this is possible only in a small percentage of patients.

#### DEFINITIONS

A few definitions are necessary before proceeding to a general discussion of the material in this paper.

<i>Classification of extent and type</i>	} follows <i>Diagnostic Standards</i> of the National Tuberculosis Association (1940 edition)
<i>of pulmonary disease</i>	
<i>Arrested</i> . . . . .	

#### "Definitely Improved"

Any inclusion of an "improved" group based on symptomatic improvement, such as reduction in temperature, gain in weight, reduction in amount of sputum, etc., would be of little help in evaluating the results of pneumoperitoneum therapy. There were certain patients, however, in whom the improvement was definite as shown by X-ray, and/or closure of cavities, and/or negative sputum, but who did not quite fulfill all the requirements to be considered as "arrested" (see X-ray case 8). Also, in certain patients, pneumoperitoneum was induced without great hope of bringing the disease to complete arrest by itself. We might reasonably expect improvement from its use to a point where some other procedure, such as thoracoplasty for instance, might be possible. Such patients fit into a "definitely improved" group, as being essentially satisfactory results of pneumoperitoneum therapy (see X-ray cases 4 and 5). To be included in this latter group, however, pneumothorax collapse must have been found impossible or unsuccessful. If pneumothorax collapse was successfully instituted, the case was classified as pneumoperitoneum "unsatisfactory". This was done to avoid criti-

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1st interspace and a 3 cm. cavity apex right lower lobe. Fibrosis throughout right upper lobe with multiple exudative lesions right base and left upper lobe. Sputum positive. Temperature to 103°F. for three days. Unable to establish right artificial pneumothorax. Pneumoperitoneum initiated 3-17-39. Temperature promptly subsided; sputum decreased; marked gain in weight. General improvement delayed by marked food allergy, finally controlled by diet.

#2. X-ray 4-8-41 shows adequate rise of diaphragm from pneumoperitoneum without phrenic. Cavity closed; marked clearing of lung parenchyma. Sputum became negative, then completely disappeared at this time. Pneumoperitoneum continued.

#3. X-ray 6-26-46. Pneumoperitoneum allowed to gradually absorb after 63 months of pneumoperitoneum collapse. Lung completely expanded. Small fibrotic scar right apex in position of previous cavity. Linear scars apex right lower lobe. Excellent general condition. Working full-time. Last follow-up examination 2-27-47, twenty months after pneumoperitoneum discontinued.





Case 4. L. S., white, female aet. 47 years. Weakness and fatigability for 3 years, attributed to menopause. X-ray chest 1942 negative. In May 1944, she was told that X-ray of chest showed a "spot in her lung." Following acute respiratory infection January 1945, productive cough and continuous fever to 104°F. Sputum positive.

§1. X-ray 2-13-45 shows tuberculous pneumonia right upper lobe. Right pneumothorax attempted unsuccessfully. Pneumoperitoneum initiated 3-5-45. Temperature gradually subsided over a period of 4 months. Clinical course uneventful.

§2. X-ray 1-6-46 shows adequate rise in diaphragm from pneumoperitoneum without

cism that pneumoperitoneum was not necessary as pneumothorax might have been done as the original procedure. (This latter is not necessarily true, however, as we have seen in far advanced bilateral cases, one side clear under pneumoperitoneum so that pneumothorax on the opposite side became possible; unilateral pneumothorax added to an existing pneumoperitoneum, or vice versa, is a much simpler procedure as far as complications are concerned, and more satisfactory as to ultimate end results, than is a simultaneous bilateral pneumothorax) (see X-ray cases 5 and 6).

The following strict definitions apply to our relatively small "definitely improved" group:

1. Cavity closed, three-day sputum negative to concentration at weekly intervals for two months, but patient on not enough exercise to be considered as "arrested", or
2. Pneumothorax attempted unsuccessfully, patient improved under pneumoperitoneum to point where thoracoplasty was possible, or
3. Tuberculous tracheo-bronchitis improved so that other therapy was possible, or
4. Extent of disease, presence of other diseases, and/or old age, precluded other collapse therapy, patient out of bed.

#### *Unsatisfactory*

1. Improved but not to point described above, or
2. Pneumothorax substituted or pneumoperitoneum abandoned for other therapy without true arrest, or
3. X-ray findings stationary or worse.

#### GENERAL DISCUSSION OF THE GROUP AS A WHOLE

##### A

This study concerns 407 consecutive patients who had pneumoperitoneum therapy initiated in the 10½ year period—February 1935 to June 30, 1945—with follow-up ending July 1946. There were 25 patients, however, who had pneumoperitoneum treatment for from 0-3 months only (see table 1). These have been eliminated from the statistical results, leaving 382 patients reported on here.

Table 1 analyzes these patients as to therapeutic results according to status of therapy, and will be discussed in detail later in the text under "results". From this table we see that pneumoperitoneum is still continued in 167 patients, with 147 arrested. Forty-one patients had pneumoperitoneum voluntarily

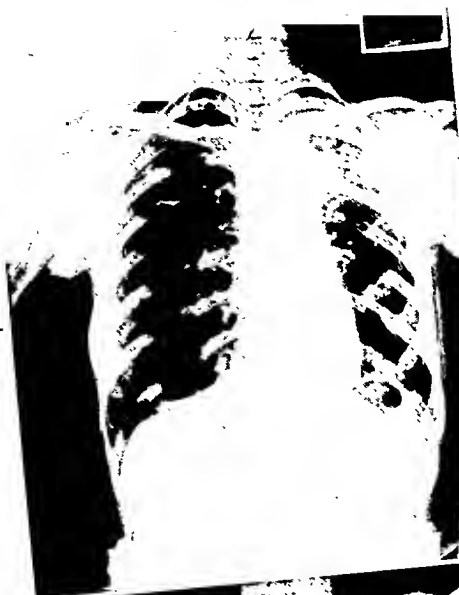
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phrenic. Lesion right upper lobe has become productive; lobe contracted; two cavities remain; lungs otherwise clear. Sputum positive. On 2-13-46 air was removed from the peritoneal cavity and a first-stage thoracoplasty (3 ribs) was done. Second-stage thoracoplasty (3 ribs) 3-19-46; uneventful recovery. Sputum consistently negative since second-stage thoracoplasty.

\*3. X-ray 4-26-46 shows adequate collapse right upper lobe from thoracoplasty. Patient remains well; has returned to a normal life regimen. Last check-up 1-17-47.

*Illustrates* improvement in a tuberculous pneumonia making an uneventful thoracoplasty possible. No spreads to any other portion of the lung.

1



2



3



4



5



6





Note that 212 (more than half) fell in the 21-40 age group. Thirty-one were between 13 and 20 years of age, and the rest (more than one-third) were 41 or over. Nearly one-fifth were 51 years or more.



CASE 6. N. G., white, female aet. 15 years. Began cough and wheezing in April 1941. Cough gradually became productive (3 oz. daily). In September 1941, X-ray was taken which showed mottling upper  $\frac{3}{4}$  right lung field and a 4 cm. cavity right apex. An acute infiltration was present off the tip of the heart left base. Sputum positive. Diagnosis: Pulmonary tuberculosis 3C with tuberculous tracheo-bronchitis. She entered Alum Rock Sanatorium 9-19-41 and a right pneumothorax was instituted 9-19-41.

#1. X-ray 10-27-41 shows inadequate right pneumothorax with atelectasis and blocked cavities right upper lobe. Infiltration right base and increase in infiltration lower  $\frac{3}{4}$  left lung field. Course downhill; daily fever to 101°F.; much wheezing from tuberculous tracheo-bronchitis; cavities right top became larger. Pneumoperitoneum initiated 12-26-41 and pneumothorax relaxed but continued. Marked improvement in all symptoms and afebrile by the end of four months. Cavities closed by July 1942. Sputum negative since August 1942 by concentration smears. Ambulatory since December 1942.

#2. X-ray 7-25-46 shows adequate rise in diaphragm from pneumoperitoneum without phrenic; small pneumothorax space right apex which is being abandoned gradually; arrest of all tuberculous lesions. Now leading a normal college life.

*Illustrates control of a very acute extensive bilateral exudative tuberculosis with multiple cavities in the right upper and extensive tuberculous tracheo-bronchitis, by a minimal pneumothorax plus an adequate pneumoperitoneum.*

### *C. Extent and Type of Pulmonary Disease*

Table 2 shows the extent and type of disease for the entire group. Note that well over one-half (56%) were far advanced, and that a large majority of the

entire group had exudative and combined lesions. Well over one-half (57%) had one or more cavities. Only 10% had minimal lesions.

#### *D. Phrenic Nerve Operations*

In the first five-year period from 1935 through 1939, phrenic nerve operations were done in 27 (49%) of a total of 55 pneumoperitoneum patients. In 15



CASE 7. R. W., white female aet. 25 years. In 1936-37 in a sanatorium in Ohio for 9 months. A right pneumothorax was initiated and maintained for 2½ years. In July 1941 she became acutely ill. Sputum positive.

#1. X-ray 7-9-41 shows a 6 cm. cavity and a 3 cm. cavity right upper lobe with acute infiltration throughout right lung. Left relatively clear. An ineffectual right basal pneumothorax was obtained and abandoned and pneumoperitoneum initiated at once. Cavities closed by 9-25-41 and sputum negative on concentration smear since that time. Ambulatory since December 1941 and full-time work from January 1943.

#2. X-ray 5-18-46 shows almost complete clearing of lesion right lung, with a few fibrous strands remaining. Adequate rise of diaphragm from pneumoperitoneum without phrenic.

(more than one-half) the phrenic operation was done at some time prior to initiating pneumoperitoneum. In contrast, during the last five and one-half-year period (1940 through June, 1945) phrenic operations were done in only 36 (10%) of a total of 352 patients, and then only for specific and rather narrow indications (see X-ray cases 1, 5, and 8). In only 9 of these patients was the phrenic surgery done prior to starting pneumoperitoneum.

A phrenic operation is not an entirely innocuous procedure. Permanent interference with the function of the diaphragm is a frequent aftermath of even

the so called temporary nerve blocks. According to our fluoroscopic and X-ray observations of the effect of pneumoperitoneum on the diaphragm in patients in



CASE 8. V. A., white, female aet. 47 years. Pulmonary tuberculosis diagnosed in September 1928. After 3 months bed rest at home she placed herself in the hands of a physician who allowed her to be up all day and gave her "intravenous treatments." In December 1932, she entered Alameda County Hospital with a 6 cm. cavity right mid-lung field. She signed herself out of the hospital in March 1934, with some improvement but positive sputum. In January 1935, she was in bed at home for 2 months and in October 1937 went to bed for 4 months following a hemoptysis.

#1. X-ray 1-13-39 shows pulmonary tuberculosis 3B, predominately productive, with 5 cm. cavity right mid-lung field and slightly smaller cavity left mid-lung field. Signs and symptoms of tuberculous tracheo-bronchitis. She finally entered Alum Rock Sanatorium 4-15-39. On May 1, 1939 a left pneumothorax was initiated but was ineffectual. With the pneumothorax she was digitalized for heart failure. The pneumothorax space was gradually lost and pneumoperitoneum was initiated 10-11-40. Cavity on right was closed by 6-9-41, reopened following respiratory infection 9-29-41, and has been finally closed since 2-21-42. A left phrenic crush was done 3-2-42. The cavity left showed very gradual improvement.

#2. X-ray 4-23-46 shows cavities closed both sides. Sputum negative from 11-7-45 until respiratory infection 10-28-46, when it became intermittently positive again. Has severe wheezing with each respiratory infection which clears very slowly. Recent x-ray 2-25-47 shows no evidence of cavitation. Pneumoperitoneum still being continued after 77 months.

whom a "temporary" phrenic nerve operation had been done years previously, the muscle continues to show signs of damage. Such permanent muscle paresis interferes with bronchial drainage and is an increased hazard if thoracoplasty

becomes necessary. Pinner, et al. (13) state that a paralyzed diaphragm also contributes considerably to impairment of pulmonary function.

We have found that a phrenic operation in most instances is not necessary to achieve the mechanical result sought. The use of an adequate pneumoperi-

TABLE 1

*Distribution of 407 pneumoperitoneum patients according to therapeutic results and status of therapy as of July 1946, showing the 25 patients eliminated from the final statistics*

STATUS OF THERAPY (PNEUMOPERITONEUM)	TOTAL	THERAPEUTIC RESULTS				ELIMINATED FROM FINAL STATISTICS*
		Arrested	"Definitely Improved"	Unsatisfactory	Dead	
Still continued.....	167	147	8	12		
Voluntarily discontinued.....	41	41				
Voluntarily discontinued prior to surgery.....	25		25			
Discontinued of necessity.....	33†	11	12‡	6§		4¶
Discontinued by pt. against advice.....	36	18	3	10		5
Discontinued by other physicians prematurely.....	17	1		10		6
Pneumothorax substituted.....	8			6		2
Dead.....	80				72	8
Total.....	407	218	48	44	72	25

\* This group of 25 patients have been eliminated from the final statistical results, as treatment here was continued only from 0-3 months, and it is felt that the therapeutic value of pneumoperitoneum cannot be judged from this short period of treatment. The largest group so eliminated, 8 dead, can be considered as errors in judgment in initiating any collapse therapy in patients so ill.

† See text re Complications (and untoward events) for analysis.

‡ Pneumoperitoneum continued for 52 months in one patient until death from coronary occlusion, not attributable to pulmonary tuberculosis or pneumoperitoneum therapy.

§ Pneumoperitoneum continued for 5 months in one patient with tuberculous pleurisy with effusion and minimal pulmonary tuberculosis until generalized spread throughout abdomen; dead with tuberculous meningitis 4 months later. Another patient dead with air embolus.

¶ Pneumoperitoneum continued 0-3 months in two patients until death (one with cerebral hemorrhage and the other from uncontrollable bleeding from gastric ulcer) not attributable to pulmonary tuberculosis or pneumoperitoneum therapy.

|| Arrested when last seen (5 are now known to be arrested; one has had recurrence; the status of 12 is unknown. These uncooperative patients make up 12 (63%) of the 19 patients not now under observation in the arrested group).

toneum alone usually gives sufficient rise of the diaphragm (see X-ray cases 2, 3, 4, 6, and 7). However, if a further rise of the diaphragm is thought to be desirable because of the lack of a favorable response of the pulmonary disease to an adequate pneumoperitoneum which has been present for at least two months, this may usually be obtained by a temporary phrenic nerve crush (at



times to a very marked degree). This additional rise will usually be maintained for as long as pneumoperitoneum is continued and possibly even after discontinuance.

TABLE 2

*Classification of extent and type of pulmonary disease prior to pneumoperitoneum therapy in 382 patients according to the Diagnostic Standards of the National Tuberculosis Association (1940 edition)*

EXTENT OF PULMONARY DISEASE AS DETERMINED BY X-RAY	TOTAL		TYPE OF PULMONARY DISEASE					
			Predom. exudative		Predom. productive		Combined	
	Num-ber	Per cent	Num-ber	Per cent	Num-ber	Per cent	Num-ber	Per cent
Minimal.....	34	10	24	6	3	1	7	3
Moderately advanced.....	135	34	56	14	25	7	54	13
Far advanced.....	213	56	64	17	39	10	110	29
Total.....	382	100	144	37	67	18	171	45

TABLE 3

*Months of bed rest before beginning routine graduated work-up regimen in 218 arrested cases according to extent of disease*

MONTHS OF BED REST	EXTENT OF DISEASE IN ARRESTED CASES					
	Minimal		Moderately advanced		Far advanced	
	Number	Per cent	Number	Per cent	Number	Per cent
0-3	21	75	58	54	13	16
4-6	5	18	32	30	29	35
7-12	1		13	12	25	30
13-81*	1		4		16	19
Total.....	28	100	107	100	83	100
Average bed rest in months.....	2.5		4.6		9.6	

\* Only two patients longer than 36 months, both far advanced and in bed for 70 and 81 months, respectively.

#### RESULTS OF ENTIRE GROUP

##### A. Results

The results in the entire group of 382 patients as of July, 1946 are as follows:

Arrested.....	218 (57%)	Satisfactory 70%
"Definitely improved".....	48 (13%)	
Unsatisfactory.....	44 (11%)	
Dead.....	72 (19%)	

1. *Months of complete bed rest (see table 3).* An analysis of results according to the extent of pulmonary disease is given later in this paper, but we wish to point out here the rather short periods of complete bed rest given in our patients

with minimal and moderately advanced disease (see table 3) who became arrested under pneumoperitoneum therapy. Note that the average for these was 2.5 and 4.6 months, respectively. Even in the far advanced cases, the average was only 9.6 months, and this was quite heavily weighted by 36 patients who were at complete bed rest for from 9-81 months (17.4 average); the remainder, 47 patients, were at complete bed rest for from 1-9 months (4.5 average).

Certain patients are included in the arrested group in whom pneumoperitoneum was substituted for pneumothorax. There were 76 such patients. In 74 patients, pneumoperitoneum was substituted early because of adhesive pleuritis, fluid in the pneumothorax space, inadequate collapse, etc., before the patient was considered arrested and out of bed. We have included these as pneumoperitoneum patients, but as a matter of fact, they are a most difficult group in which to expect good results. When a primary procedure has failed or can no longer be used, results from any secondary procedure should, in the long run, be less adequate than if this secondary procedure were the one of primary election. This may indicate that in many of these cases where pneumothorax was our procedure of first choice, pneumoperitoneum should have been done as the initial procedure.

In only 2 of these patients was pneumoperitoneum substituted later after the patient was up and about. In these, the period of pneumothorax was considered inadequate and additional collapse was deemed necessary. Pneumoperitoneum was induced without any additional bed rest. These patients progressed well and are considered as satisfactory pneumoperitoneum results. It is this small group which accounts for "no bed rest" being given in certain pneumoperitoneum patients.

2. *Treatment in addition to pneumoperitoneum.* Every patient in this group had a period of tuberculosis sanatorium care. We believe that this is essential for the education of the patient and family and, with us, the main purpose of the sanatorium stay is for such education. In most of these patients, the period of institutional care was 2 months at the most, as their homes were adequate and we are able to provide medical care with a complete bed rest regimen in their own homes. This is accomplished by home visits as often and as long as necessary, with the use of a portable fluoroscope which is constantly available and regularly used. Adequate isolation precautions are not difficult.

The period of complete bed rest can be greatly reduced by adhering strictly to the following criteria: sputum absent or negative to three-day concentration weekly for two months; cavity, if any, closed and pulmonary disease by X-ray apparently stable. It is at this point that we start our patients thinking about rehabilitating themselves. We begin active and on the whole highly successful efforts in this direction. We do not consider the patient is well because of what we may think of his capacity for work, but only when he has returned to, and remains at, a productive occupation.

### *B. Complications (and Untoward Events)*

We have had practically all the complications that one can have in connection with pneumothorax (except for loss of function due to thickening of the pleura

and a non-expansile lung) as well as some inherent in the anatomy of the abdominal wall and its contents. Purely by chance, we have had no patient with acute appendicitis in this group. The complications, however, have not been such as to deter us from using the procedure. They have been minimal in number and not alarming in extent.

*Ascites.* As might be expected from pneumothorax experience, fluid in the peritoneal cavity was a common complication. Each patient was fluoroscoped before and after each office or sanatorium treatment, and frequently when confined to bed at home. At any time ascites, usually asymptomatic, might be noted, from small to quite considerable amounts. As time went on, experience led us to pay little attention to these. The fluid will usually be absorbed in a period of weeks or months. It may recur in the same patient. An occasional patient may have malaise and fever for several days at the time the ascites appears, but with symptomatic treatment and reassurance, the pneumoperitoneum usually can be continued. In only 4 patients (see following list) in this group was pneumoperitoneum discontinued for ascites alone without obvious infection. The gross and microscopic character of this fluid is essentially that found in pleural effusions.

*Hernia.* Preexisting herniae of the abdominal wall, or those brought to light after the induction of pneumoperitoneum were the cause of abandoning the procedure in only one instance. A properly selected truss will relieve discomfort. The hernia can always be repaired after pneumoperitoneum is stopped. This is a small price to pay for the control of such extensive pulmonary tuberculosis as existed in most of these cases.

*Discomfort.* Discomfort and abdominal pain is a common complaint of patients early in the course of pneumoperitoneum. If this is considered as one of the usual accompaniments of the procedure and minimized by the physician, one rarely has occasion because of this to modify in any degree the procedure itself. The discomfort practically always disappears, usually within six weeks. It is amazing what people with pneumoperitoneum can do at times. We have 3 patients who ride horseback (with our approval) still carrying a pneumoperitoneum.

*Cardiac embarrassment.* In older people, if pneumoperitoneum is pushed too rapidly or the diaphragm raised too high, circulatory embarrassment may be noted. This is noted especially where marked emphysema is present, although we have had to discontinue therapy in only 2 instances. The pneumoperitoneum refills may be reduced in amount but not in frequency. The procedure can then usually be continued.

Pneumoperitoneum was discontinued of necessity in 33 (8%) patients (see tables 1 and 5). Of these, 5 were untoward events occurring in patients receiving pneumoperitoneum therapy, rather than being complications of the therapy itself, as follow:

Coronary occlusion (dead).....	1
Cerebral hemorrhage (dead).....	1
Uncontrollable bleeding from gastric ulcer (dead).....	1

Thrombosis of the deep saphenous veins.....	1
Subacute nephritis associated with signs of cardiac failure (far advanced pulmonary tuberculosis, immense cavitation, of 11½ years standing; obesity)...	1

In the 407 patients, the percentage of complications severe enough so that pneumoperitoneum was discontinued varies from under 6% to about 7%, depending on the view-point. There were 28 (7%) patients in whom such complications developed as follows:

Adhesive or obliterative peritonitis.....	8
Nausea, pain (one of these eliminated in subsequent statistics of results as having had pneumoperitoneum only 0-3 months).....	4
Ascites (one of these eliminated in subsequent statistics of results as having had pneumoperitoneum only 0-3 months).....	4
Pelvic inflammatory disease (exacerbation) (one possibly tuberculous; all recovered).....	3
Cardiac embarrassment (cor pulmonale) (one dead of pulmonary tuberculosis 5 months later; other dead of pulmonary tuberculosis and cardiac failure 3 years later).....	2
Tuberculous peritonitis.....	1
Generalized abdominal spread; tuberculous meningitis (dead).....	1
Umbilical hernia.....	1
Torsion of omentum.....	1
Hemorrhage in spleen (surgical repair).....	1
Diaphragm too high after phrenic crush.....	1
Air embolism (dead).....	1

Not all of the above are complications of pneumoperitoneum. Several are attributable to tuberculosis as a disease. One such is the case of tuberculous peritonitis, which, as has been shown (3) and we believe, occurs no more frequently during pneumoperitoneum therapy than would be expected in a like number of patients with tuberculosis whatever the therapy. Another is the case of generalized tuberculosis, ending in death with tuberculous meningitis. There is also another group, the 3 patients who developed exacerbation of pelvic inflammatory disease, in which it is doubtful whether pneumoperitoneum played any significant role. Eliminating these 5 patients drops the percentage of complications to under 6%.

It will be noted that there was only one death directly attributable to pneumoperitoneum therapy. The majority of the complications were not serious and played no part in the patients' subsequent course. Nine of the complications occurred after the tuberculosis was arrested, and all of these patients, except for one recurrence, are leading a normal life. Another 9 patients have continued as "definitely improved". Eight patients, without the deaths from tuberculous meningitis and air embolism, were unsatisfactory results with regard to their pulmonary tuberculosis, and in 6 of these the complication played no part in their subsequent course.

#### *C. Sputum (see Table 4)*

Of the total number of 382 cases reported, there were 291 (76%) with positive sputum (direct and concentration) at some time while under our care.

### D. Results for Entire Group According to the Duration of Therapy

Table 5 shows the results of pneumoperitoneum for the entire group with reference to duration of therapy in months. Seventy per cent of those who were so treated for longer than one year are arrested.

### E. Selection of Patients as Affecting Results

Patients with pulmonary tuberculosis suitable for pneumoperitoneum therapy fell into two groups:

First (a favorable group) patients in whom pneumoperitoneum was used as the most desirable collapse procedure in itself without attempting other collapse therapy; and Second (an unfavorable group) patients in whom pneumoperitoneum was used because collapse was considered advisable, and:

a. other collapse therapy tried and found impossible or unsatisfactory; or

TABLE 4

*Results of sputum examinations\* in 382 patients, according to extent of disease*

EXTENT OF DISEASE	TOTAL	SPUTUM POSITIVE	
		Number	Per cent
Minimal.....	34	17	50
Moderately advanced.....	135	76	56
Far advanced.....	213	198	93
Total.....	382	291	76

\* Direct and concentration smears only in the majority, at some time while under our care.

- b. lesions considered too extensive for other satisfactory collapse therapy (see X-ray case 5); or
- c. tuberculous tracheo-bronchitis precluded pneumothorax (see X-ray case 5); or
- d. silico-tuberculosis present; or
- e. emphysema and/or old age was present; or
- f. tuberculous pneumonia (see X-ray case 4); or
- g. a combination of some of above.

The "favorable group" of 66 patients (see table 6) comprised 29% of the patients which resulted in arrest, none of the "definitely improved" group, and 3% of the unsatisfactory and dead group. We attained arrest in 94% of the group so chosen. They include one-half of the minimal patients, about one-third of the moderately advanced, and only 2 of the far advanced. We chose, of the 47 moderately advanced, 38 without cavity and 5 with single cavity 2 cm. or less in diameter. If we considered the past few years alone, we would have a much higher percentage of minimal cases, as we now use pneumoperitoneum as the procedure of choice in minimal tuberculosis, particularly if the disease is an exudative lesion in a highly susceptible individual. Our experience with ob-

TABLE 5

Results as of July 1946, in 407 consecutive cases by status of therapy according to the duration of pneumoperitoneum in months

DURATION OF PNEUMOPERI- TONEUM	TOTAL	RESULTS																Dead
		Arrested						"Definitely improved"					Unsatisfactory					
		Total	Still cont. <sup>a</sup>	D.C. vol.	D.C. of nec.	D.C. by pt.	D.C. other phys.	Total	Still cont.	D.C. vol. <sup>b</sup>	D.C. nec.	D.C. by pt.	Total	Still cont.	D.C. nec. <sup>c</sup>	D.C. by pt.	D.C. other phys.	
<i>mo.</i>																		
0-3 <sup>d</sup>	25												17		6 <sup>e</sup>	5	6	8
4-6	30	4			1	3		6		2	2	2	11		3 <sup>f</sup>	6	2	9
7-12	61	11	5		1 <sup>g</sup>	4	1	9	1	6	2		10	1	4	1	4	31
13-24	114	57	43	2	4	8		25	4	16	4	1	14	4	4	3	3	18
25-36	53	43	34	5	3	1		2	1		1		2		1		1	6
37-48	54	42	35	6		1		3	1		2		4	4				5
49-60	35	33	17	15	1			1			1 <sup>h</sup>		1	1				
61-72	23	18	9	7	1	1		1		1			2	2				2
73-84	4	4	2 <sup>i</sup>	2														
85-96	6	5	1	4														1
97-108	1	1	1															
10 yrs.	1							1	1									
Total.....	407	218	147	41	11	18 <sup>i</sup>	1	48	8	25	12	3	61	12	18	15	16	80

<sup>a</sup> 12 months minimum follow-up.

<sup>b</sup> Discontinued voluntarily as "definitely improved" to the point where thoracoplasty indicated.

<sup>c</sup> The group of 8 cases in which pneumothorax was substituted have been added to this column.

<sup>d</sup> Eliminated from final statistics. See table 1, footnote \*. Note also under this group that in the 17 patients listed as unsatisfactory at the time pneumoperitoneum was discontinued, 7 additional patients are now known to be dead but did not die within the 0-3 months treatment period.

<sup>e</sup> See table 1, Footnote ¶.

<sup>f</sup> See table 1, Footnote §.

<sup>g</sup> Four patients had sputum converted, clearing of lesions by x-ray, and were nearing the N.T.A. classification "arrested" when pneumoperitoneum was discontinued (in 3 by the patient, and in 1 because of complications). These patients were followed from 8-31 months and were "arrested" when last seen.

<sup>h</sup> See table 1, Footnote ‡.

<sup>i</sup> These patients in the long time "still continued" therapy brackets have reached arrest only after a long time. None of them have received therapy for as long as five years after reaching arrest (see X-ray case #8).

<sup>j</sup> See table 1, Footnote ||.

servation alone in these patients is not satisfactory, contrary to recent reports (14).

The "unfavorable group" of 316 patients (see table 6) comprised 71% of the cases which resulted in arrest. We attained arrest in 49% of the group so chosen. These were patients in whom collapse therapy was considered advisable but who showed the following problems (grouped as to the major problem):

1. Other collapse therapy tried and found impossible or unsatisfactory..... 165
2. Lesions considered too extensive for other collapse therapy..... 100
3. Tuberculous tracheo-bronchitis precluded pneumothorax..... 32
4. Silico-tuberculosis..... 9
5. Emphysema and/or old age (51-72 years)..... 7
6. Tuberculous pneumonia..... 3

TABLE 6

*Results in 582 patients according to extent of pulmonary disease and whether pneumoperitoneum was chosen as the most desirable collapse procedure in itself (favorable group), or was chosen only as the best available collapse procedure (unfavorable group)*

EXTENT OF DISEASE IN FAVORABLE AND UNFAVORABLE GROUPS	TOTAL	RESULTS							
		Arrested		"Definitely improved"		Unsatisfactory		Dead	
		Num-ber	Per-cent*	Num-ber	Per-cent*	Num-ber	Per-cent*	Num-ber	Per-cent*
Favorable group									
Minimal.....	17	16	94	0		1		0	
Moderately advanced.....	47	44	94	0		2		1	
Far advanced.....	2	2		0		0		0	
Total.....	66	62	94						
Unfavorable group									
Minimal.....	17	12	71	2		1		2	
Moderately advanced.....	88	63	72	8		6		11	13
Far advanced.....	211	81	38	38	18	34	16	58	27
Total.....	316	156	49	48	15	41	13	71	22

\* The percentage of the total number of patients in the specified "extent of disease" group.

As shown above, the good results with pneumoperitoneum therapy were not obtained in simple forms of tuberculosis only. In the main, there were serious problems involving extensive and complicated forms of the disease. The initial prognosis of most of these patients was extremely poor.

To further clarify the type of patient in the largest "unsatisfactory" group, "other collapse therapy tried and found impossible or unsatisfactory", we find that pneumothorax was tried first in 160 of the 165 patients, and thoracoplasty in 5. Pneumothorax was found impossible to initiate, or was or became inadequate and was abandoned, in 114, leaving the large majority of these patients in no better condition, or possibly worse, than when pneumothorax was first considered advisable. An additional 16 patients had inadequate pneumothorax with

spread of the disease in the same or the opposite lung when pneumoperitoneum was initiated. Another 19 cases had an adequate collapse, but a spread to the contralateral side. There were 10 cases in which empyema complicated the pneumothorax, some with recognizable bronchial fistulae; oleothorax had been substituted for pneumothorax in 4, three with spread of the disease before pneumoperitoneum was initiated. In one case, an atelectatic lung led us to abandon the pneumothorax in favor of pneumoperitoneum. As to the 5 cases of thoracoplasty which were followed by pneumoperitoneum therapy, 4 were inadequate, one with spread to the same side and one with repeated hemoptysis, where further surgery was deemed inadvisable. One case was an adequate thoracoplasty with spread to the contralateral side.

#### ANALYSES OF CLINICAL STATUS

##### *A. Arrested Group*

As seen under "Results of Entire Group", in the group as a whole there were 218 patients (57%) arrested (see also table 1).

1. *Pneumoperitoneum still continued.* Of the 167 patients, 147 (88%) are arrested. The 147 patients still under treatment are 67% of the arrested group. Table 5 shows the duration of therapy in months. One hundred and twenty-five have returned to a normal working life (see X-ray cases 6 and 7). The present condition of 6 patients is unknown, but fitted into this classification when last seen. By definition, none of this arrested group are ill with exacerbations, but 7 patients (5%) had recurrence while under treatment and are again arrested following an additional period of bed rest with continued pneumoperitoneum. Six of these had bilateral lesions (5 with cavitation). This may show that our primary bed rest was not long enough in these particular patients. These exacerbations occurred between 6 and 22 months after the beginning of pneumoperitoneum therapy, except in one instance where breakdown occurred at 52 months.

2. *Pneumoperitoneum voluntarily discontinued.* Pneumoperitoneum therapy is still so new that even with the time covered in this report, we can present only 41 arrested patients (18%) in whom the therapy was voluntarily discontinued (see X-ray cases 1, 2, and 3). In the first 5 years or "introductory" phase, up to 1940, we used pneumoperitoneum in only 55 cases, and in those not with all of our present indications. Tables 5 and 7 show the duration in months, and follow-up data in the arrested voluntarily discontinued patients. All but 7 of these patients were treated for 3½ years or more.

Two patients had exacerbation of their tuberculosis six months later, and are again arrested under pneumoperitoneum treatment. Including these 2 patients up to the time of their breakdown, 39 (95%) have been leading a normal working life for from 18 to 110 months; two have slight restrictions only; none are restricted severely.

This group was further analyzed with reference to the extent of their disease prior to treatment. This is shown in table 8. Comparing the extent of the pulmonary disease of the entire group (see table 2) and the arrested group volun-



tarily discontinued, it is seen that a slightly higher percentage of the minimal and moderately advanced, and a slightly lower percentage of the far advanced were voluntarily discontinued (see Graph A).

3. *Pneumoperitoneum discontinued because of necessity.* Tables 5 and 7 show the statistics as regards duration of therapy and follow-up in the arrested pa-

TABLE 7

*Follow-up in months to the most recent examination up to July 1946, in the 215 cases in which pneumoperitoneum was discontinued\**

TIME FOLLOWED AFTER PNEU- MOPERITONEUM DISCONTINUED	DISCONTINUED VOLUNTARILY		DISCONTINUED OF NECESSITY				DISCONTINUED AGAINST ADVICE			
	Total	Arrested	Total	Arrested	Defi- nitely im- proved	Unsatis- factory	Total	Arrested	Defi- nitely im- proved	Unsatis- factory
mo.										
0-3	4	4	5	1	2	2	19	7	2	10
4-6	6	4†	3	0	1	2	0	0	0	0
7-12	13	13	2	1	0	1	3	3	0	0
13-24	12	12	8	3	3	2‡	4	3	1	0
25-36	5	5	9	0	0	0	5	4	0	1§
37-48	0	0	3	1	2					
49-60	0	0	3	3	0					
61-72	0	0	2	0	2					
73-84	0	0	0	0	0					
85-96	0	0	1	1	0					
97-103	1	1	1	0	1					
10 yrs.			1	0	1					
Total	41	39	29	10	12	7	31	17	3	11

\* Not shown in the table are the following:

Under "discontinued voluntarily", 25 cases "definitely improved" to the point where thoracoplasty indicated (see text under "analyses of clinical status; B, 'definitely improved' group" for these).

Eleven cases "discontinued by another physician prematurely". One remains arrested for 18 months after 7 months of pneumoperitoneum; the others are unsatisfactory.

Six cases in which pneumothorax was substituted.

Seventy-two dead.

For the 167 still continued, see table 5.

† Two patients (5%) had recurrence of their tuberculosis six months after pneumoperitoneum discontinued voluntarily. Pneumoperitoneum immediately re-instituted and patients are again arrested under treatment.

‡ One patient with recurrence, now under pneumothorax collapse.

§ One patient is known to have had recurrence.

tients in whom pneumoperitoneum was discontinued because of necessity. Suffice it to say that these 11 patients had pneumoperitoneum for from 4 to 69 months. Nine are known to be arrested; the present status of 1 is unknown but was arrested when last seen. Nine have been working from 1 to 100 months. There has been one recurrence.

4. *Pneumoperitoneum discontinued by patient against advice.* Tables 5 and 7

show the statistics as regards duration of therapy and follow-up in the arrested cases where pneumoperitoneum was discontinued against advice. Of these 18, pneumoperitoneum was given from 4 to 70 months, and all were arrested when last seen; seventeen were working. However, only 5 are now known to be arrested; the present status of 12 is unknown; and 1 is known to have had recurrence of his tuberculosis.

These uncooperative patients make up 12 (63%) of the 19 cases not now under observation in the arrested group.

TABLE 8

*Analysis of extent of initial pulmonary disease in the 41 arrested patients in whom pneumoperitoneum was voluntarily discontinued*

DESCRIPTION OF PULMONARY DISEASE	EXTENT OF DISEASE		
	Minimal	Moderately advanced	Far advanced
Unilateral lesion without cavity.....	3*	4	2†
Unilateral lesion with single cavity			
Top.....			4
Bilateral lesions without cavity.....	3‡	11	2
Bilateral lesions with single cavity			
Top.....		2	1
Mid.....			2
Base.....		1	2
Bilateral lesions with multiple unilateral cavities			
Top and Mid.....			2
Mid and Base.....			1
Bilateral lesions with bilateral cavities			
Top.....			1
Total			
Number.....	6	18	17
Per cent.....	15	44	41

\* Two patients with tuberculous tracheo-bronchitis and minimal pulmonary involvement.

† One complicated with tuberculous tracheo-bronchitis.

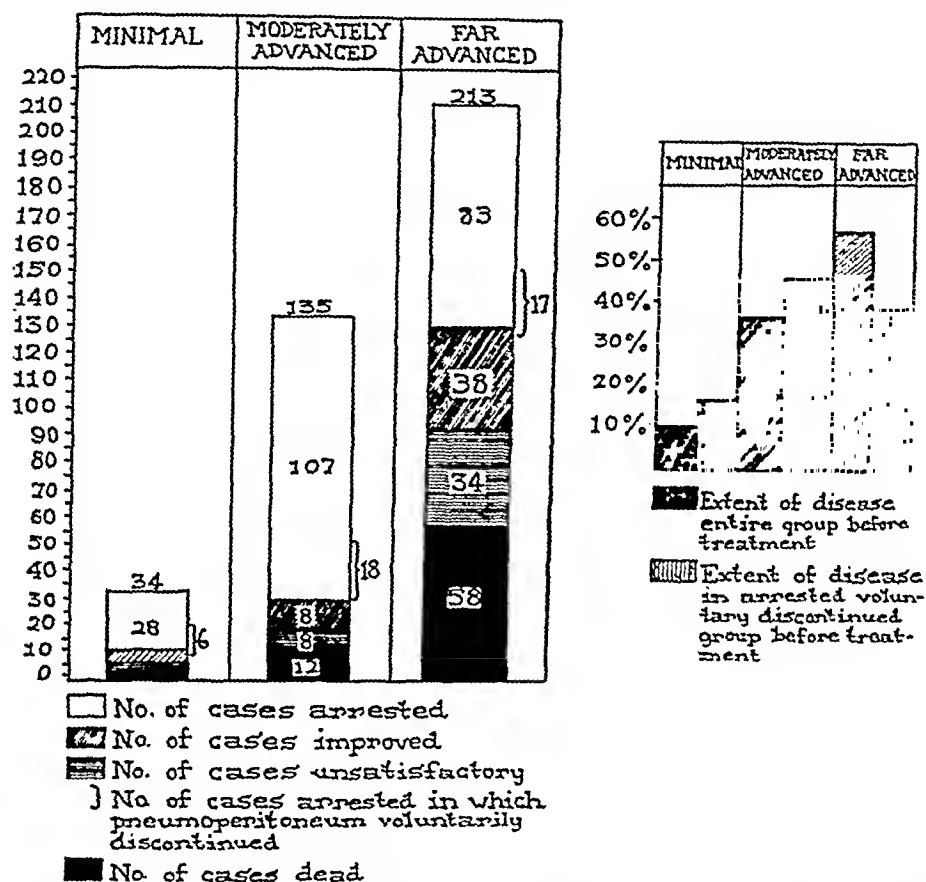
‡ One with tuberculous tracheo-bronchitis and minimal pulmonary involvement.

5. *Pneumoperitoneum discontinued prematurely.* Treatment in 1 case was discontinued by a physician after what we consider an inadequate period of time. The patient had pneumoperitoneum for 7 months, at which time he was considered arrested. Follow-up shows he has been out of bed 17½ months; working 12½ months; no exacerbation to date; no restrictions.

#### B. "Definitely Improved" Group

Results of the entire group show 48 patients in the "definitely improved" group (13%). Seventy-nine per cent were far advanced (see tables 1, 5, 6, 7, and definition page).

1. Of these, 25 (52%) (see table 5, voluntarily discontinued) were judged ready for thoracoplasty after having had pneumoperitoneum from 4 to 66½ months (average 19.2 months). (See X-ray cases 4 and 5.) Twenty-one (84%) were far advanced, with 9 patients having a complicating tuberculous tracheo-bronchitis. One uncooperative patient refused surgery and discontinued pneumoperitoneum at that time, but returned one year later and pneumoperitoneum



GRAPH B, left. Comparison of the initial pulmonary disease of the entire group of 382 patients with that of the 41 cases in which pneumoperitoneum was voluntarily discontinued.

GRAPH A, right.

was reestablished. There were 5 recurrences following surgery: 3 were on the opposite side and pneumoperitoneum was reestablished with the patients now arrested under pneumoperitoneum therapy; 2 were late recurrences: one, 2 years later, cavity opposite side and pneumoperitoneum reestablished with negative sputum and closure of cavity; and one, 16 months later, cavity reopened, pneumoperitoneum reestablished with negative sputum and closure of cavity.

2. Five patients were not on quite enough exercise to be classified as arrested.

3. There were 18 patients included in the "definitely improved" group in whom age and/or the patient's condition precluded surgery or other collapse

therapy, who showed definite (not just symptomatic—see definition page) improvement under pneumoperitoneum therapy, and were out of bed (see X-ray cases 5 and 8). One of these died of coronary occlusion after 52 months of treatment.

### C. Unsatisfactory Group

(See tables 1, 5, 6, 7, and definition page.)

There are 44 (11%) patients in the unsatisfactory group. Pneumothorax was substituted in 6; there were 4 with silicotuberculosis, one with tuberculous pneumonia, and in 17 a tuberculous tracheo-bronchitis played a large part. (Also see text and tables 10, 11 and 12 on cavitation and size of cavities.)

TABLE 9

*Therapeutic results in 382 patients according to extent of disease*

EXTENT OF DISEASE	TOTAL	RESULTS											
		Arrested			Definitely improved			Unsatisfactory			Dead		
		Num-ber	Per cent of total ar- rested	Per cent of each group	Num-ber	Per cent of total def. impr.	Per cent of each group	Num-ber	Per cent of total unsat.	Per cent of each group	Num-ber	Per cent of total dead	Per cent of each group
Minimal.....	34	28	13	82	2	4	6	2	5	6	2	3	6
Moderately advanced....	135	107	49	79	8	17	6	8	18	6	12	17	9
Far advanced.	213	83	38	39	38	79	18	34	77	16	58	80	27
Total.....	382	218	100		48	100		44	100		72	100	

### D. Dead Group

(Tables 1, 5 and 6.)

There are 72 (19%) patients whose disease was progressive even under treatment and eventually died. There were 3 with silico-tuberculosis, and in 16 a tuberculous tracheo-bronchitis played a large part. (Also see text and tables 10, 11, and 12 on cavitation and size of cavities.)

## OTHER ANALYSES OF INTEREST

### A. Extent of Pulmonary Disease

In analyzing the results according to the extent of pulmonary disease (table 9), of the 34 patients with minimal pulmonary tuberculosis (10% of the entire group of 382 cases), 28 (82%) were arrested with pneumoperitoneum therapy; of the 135 moderately advanced (34% of the entire group), 107 (79%) were arrested; and of the 213 far advanced (56%) of the entire group, 83 (39%) became arrested. From the excellent results obtained in the cases with minimal and moderately advanced disease as compared with those in the far advanced group, it is obvious that pneumoperitoneum therapy, like bed rest alone, is most effective

in the cases where the disease is not too far advanced. When one considers the economic saving alone, to the patient, because of the shortened period of complete bed rest necessary when pneumoperitoneum is used (see table 3), not to mention the low exacerbation and recurrence rate (see text), the more rapid conversion of sputum, and always the opportunity of changing to a more radical type of therapy should the need occur, then the advantages of pneumoperitoneum become even more striking.

TABLE 10

*Results in 135 patients having moderately advanced tuberculosis with and without cavitation*

CAVITATION	TOTAL		RESULTS				
			Arrested		Definitely improved	Unsatisfactory	Dead
	Number	Per cent	Number	Per cent of each group	Number	Number	Number
With.....	45	33	33	73	3	4	5
Without.....	90	67	74	82	5	4	7
Total.....	135	100	107		8	8	12

TABLE 11

*Results in 213 patients having far advanced tuberculosis with and without cavitation*

CAVITATION	TOTAL		RESULTS							
			Arrested		Definitely improved		Unsatisfactory		Dead	
	Number	Per cent	Number	Per cent of each group	Number	Per cent of each group	Number	Per cent of each group	Number	Per cent of each group
With.....	178	84	73	41	37	21	26	15	42	24
Without.....	35	16	10	29	1		8		16	46
Total.....	213	100	83		38		34		58	

Further, pneumoperitoneum can be initiated in nearly all patients (not true of pneumothorax); it is a completely reversible procedure in that it can be stopped at any time without complications (not true of pneumothorax, where there is a real danger of a non-expansile lung); it can be reinstituted if necessary (again usually not true of pneumothorax); and, there is a relative lack of important complications.

In the far advanced cases, the result of 39% arrested is significant therapeutically, especially when it is seen (table 3) that 81% of the cases who became arrested were confined to bed for not more than 12 months. It is usually indicated within the first 3 to 6 months whether or not pneumoperitoneum therapy is going to be effective. Also, if to the arrested cases in the far advanced group

is added the 38 (18%) patients who were "definitely improved" (see strict definition), 57% fall into a group which might be regarded as satisfactory, considering the serious problems that many of these patients presented. (See text under "Selection of patients 'unfavorable group'", table 6; text and tables 10, 11, and 12 on cavities.)

Graph B shows the results in 382 cases as compared with the extent of pulmonary disease.

The composition of each of the four groups of results (Arrested, "Definitely Improved", Unsatisfactory, and Dead), according to the extent of disease in each, also can be seen in table 9. In the arrested group, we find minimal 13%,

TABLE 12

*Results in 223 patients with cavitation, according to the size of the cavities (total diameters), and whether single, or multiple (divided as to unilateral or bilateral)*

CAVITATION—SIZE AND WHETHER SINGLE, OR MULTIPLE UNILATERAL OR BILATERAL	TOTAL	RESULTS		
		Arrested	Definitely improved	Unsatisfactory and dead
Single				
5 mm.—2 cm.....	56	43	2	11
2.1 cm.—4 cm.....	60	27	16	17
4.1 cm.—8 cm.....	9	4	2	3
Larger.....	5	1	3	1
Multiple (combined diameter)				
Unilateral				
Under 4 cm.....	5	2	0	3
4 cm.—8 cm.....	20	12	4	4
Larger.....	14	3	4	7
Bilateral				
Under 4 cm.....	1	1	0	0
4 cm.—8 cm.....	20	7	3	10
Larger.....	33	6	6	21
Total.....	223	106	40	77

moderately advanced 49%, and far advanced 39%. In the other three groups the percentages are very close to each other, and show minimal about 4%, moderately advanced about 18%, and far advanced about 79%. The arrested group contains a higher percentage of minimal and a much higher percentage of the moderately advanced cases as compared with the "definitely improved", unsatisfactory, and dead groups, which contain a very much higher percentage of the far advanced.

1. *Results in minimal lesions related to sputum findings.* This group of 34 cases was studied as to any difference between sputum positive and sputum negative cases, according to results obtained with pneumoperitoneum. It has been relatively recent that gastric lavage and guinea pig inoculations have been routine, so the earlier patients in this group were negative on concentration test only. It is interesting to note that the patients were equally divided (17 to 17)

and that the results also were exactly the same: In each group, Arrested 14, "Definitely Improved" 1, Unsatisfactory 1, and Dead 1. (In the unsatisfactory case with negative sputum, pneumothorax was substituted after 13 months as the disease was progressive. One death was due to tuberculous tracheo-bronchitis and progressive disease; and the other (negative sputum) to a generalized tuberculosis 5½ months after treatment started.)

2. *Results in moderately advanced disease related to cavitation.* The 135 cases of moderately advanced disease are tabulated according to those with cavity and those without (see table 10). There were 45 (33%) patients with cavitation, and 90 (67%) without. Results show only a slight difference (9 points) in favor of those without cavity (arrested 82%; 73%).

3. *Results in far advanced disease related to cavitation.* Of the 213 cases of far advanced disease, those with cavity numbered 178 (85%) and those without numbered 35 (16%) (see table 11). Interestingly enough, here 41% with cavity were arrested as compared with only 29% without cavity. With cavity, 39% were unsatisfactory and dead as compared with 69% without cavity. This is attributed to the fact that our far advanced cases without cavity were those with very acute and massive involvement, many with tuberculous tracheo-bronchitis.

### B. Cavitation

1. 223 (58%) patients with cavitation in the entire group of 382 patients. The following list shows the therapeutic results as of July 1946:

Arrested.....	106 (47%)	} Satisfactory 65%
"Definitely improved".....	40 (18%)	
Unsatisfactory.....	30 (15%)	
Dead.....	47 (20%)	

Table 12 shows the size of cavities for each patient, and whether single, or multiple (divided as to unilateral or bilateral), according to clinical status (see also tables 8, 10 and 11.)

In the arrested group, there were 75 (71%) with single cavities, and only 31 (29%) with multiple cavities. In comparison, the unsatisfactory and dead group showed a much higher percentage of multiple cavities: 45 (58%) patients.

Again, in the arrested group, 73 patients (69%) had cavities with a total diameter of not more than 4 cms. as compared with 31 patients (40%) in the unsatisfactory and dead group; or, of the 122 patients with such cavities, 60% became arrested, and another 15% "definitely improved".

When we include all of the patients with cavities totaling not more than 8 cm. in diameter, we find that with a total of 171 such patients, 96 (56%) became arrested (see X-ray cases 2 and 3), and another 27 (16%) were "definitely improved". On the other hand, in the 52 patients with cavities larger than 8 cm., only 10 (19%) became arrested (see X-ray cases 7 and 8), with an additional 13 patients (25%) "definitely improved".

In summary, in the treatment of patients with cavitation by pneumoperi-

toneum, the best results are found with the single cavities, but the results are good (56% arrested) in all cavities whose total diameter does not exceed 8 cm. At this point there is a sharp decline in the expectancy of arrest.

2. *Total number of cavities*—357. The actual total number of cavities present was more than the figure given above, as in tabulating our statistics, multiple small cavities located in the same part of the lung were considered as one large cavity (e.g.—a 2 cm. and 3 cm. cavity in the middle lung field was tabulated as “one 5 cm. cavity, mid”). Also, we would like to point out that in the following figures, patients who had multiple cavities (for instance, one apical and one basal) were considered as cavity closure only if the disease became arrested and *both* cavities responded, as we did not tabulate each individual cavity as to closure. Not infrequently, one of such cavities would be closed by pneumoperitoneum, but if another remained open, the case would be classified as unsatisfactory. It is obvious that there were actually more cavities closed than is shown by this use of the arrested group, but in spite of this, the figures bring out the effectiveness of pneumoperitoneum (arrested 142 (40%) and “definitely improved” another 61 (17%).

The position of the cavity within the lung,<sup>1</sup> whether apical, in the mid-lung field, or basal has little bearing on the results which may be expected from pneumoperitoneum therapy. The percentages of each group, those arrested, improved, and unsatisfactory and dead, as compared with the three separate locations of the cavity, are extremely close with slightly more favorable results with the basal cavities in this series. The figures are: 230 apical, 107 mid-lung, and 20 basal cavities; arrested, 41% apical, 37% mid-lung, and 40% basal; definitely improved, 17% apical, 15% mid-lung, and 25% basal; unsatisfactory and dead, 42% apical, 48% mid-lung, and 35% basal. The small number of basal cavities makes the difference statistically unreliable with regard to these alone, but the figures bring out clearly the response throughout the entire lung to adequate rise of the diaphragm.

### C. *Tuberculous Tracheo-bronchitis*

This was an initial diagnosis in 74 patients (19%) as a complication of clinical significance on the basis of symptoms plus physical examination and/or X-ray findings, with bronchoscopy in some to localize the extent and character of the lesions. We have shown (15) that most tuberculous tracheo-bronchitis of clinical significance is diagnosable without bronchoscopy. Bronchoscopy is necessary to classify the kind of lesion and its extent.

Compared with cases with cavity (see text), the results in this group were definitely not good (arrested 27, or 36%; definitely improved 18, or 25%). Compared with any other treatment available during the period covered by this study, the results with this complication in the minimal and moderately advanced cases of pulmonary tuberculosis were not unsatisfactory (see X-ray cases 5, 6, and 8). Of 29 cases, 6 minimal and 13 moderately advanced, 65% were arrested and only 2 cases were in the unsatisfactory and dead group. Most of this work, of course, antedates use of promine and streptomycin.



*D. Pleurisy with Effusion Complicating the Initial Pulmonary Tuberculosis*

When the patient has his pulmonary tuberculosis complicated by a pleural effusion, we remove the fluid, and when the pulmonary lesion warrants, replace with air to continue a pneumothorax collapse. Complications, especially non-expansile lungs, are common in these patients. More recently we have been using pneumoperitoneum in certain of these problems, especially in minimal lesions, or where patients without a demonstrable parenchymal lesion by X-ray show positive stomach wash by guinea pig inoculation or culture.

Results have been gratifying (see table 13) with 80% arrested. All except one of these arrested patients were followed for from 2-8 years, and, although the total number of cases is small, this percentage arrested is much higher than our own figures show in a like follow-up period for primary pleurisy with effusion

TABLE 13

*Results in 15 patients with a complicating pleurisy with effusion according to the extent of pulmonary disease*

PLEURISY WITH EFFUSION AND EXTENT OF PULMONARY DISEASE	TOTAL	RESULTS		
		Arrested	Definitely improved	Unsatisfactory and dead*
Minimal.....	6	4	0	2
Moderately advanced.....	6	6	0	0
Far advanced.....	3	2	1	0
Total				
Number.....	15	12	1	2
Per cent.....		80		

\* One patient with tuberculous tracheo-bronchitis, progressive disease, and one dead with a generalized tuberculosis with meningitis after 8½ months.

without demonstrable parenchymal involvement treated with a strict six months bed rest regimen alone.

*E. Silico-tuberculosis*

Our results in silico-tuberculosis were in general unsatisfactory, as is the common experience with all methods of treatment to date. In 10 cases, 2 arrested, one improved, 4 unsatisfactory, 3 dead.

## DISCUSSION

In the treatment of pulmonary tuberculosis, complete bed rest is the foundation upon which the physician builds. In addition to this, collapse therapy of various kinds is used to provide local rest to some portions of the lung to initiate healing of the diseased process, to correct an unfavorable mechanical situation such as the presence of a cavity in the lung parenchyma, or to speed up the healing process. With the addition of collapse therapy one may shorten the time of

complete bed rest, allowing the patient to be ambulatory and return to a productive occupation at an earlier date.

With each patient at some point during the course of his disease, the attending physician must make the decision whether or no he will use collapse therapy in this particular patient. If he chooses to use collapse therapy, he must then decide which type will best produce the result he is trying to achieve. Does he want the procedure to be reversible? If so, which method is not only the most likely to control the lesion but also return the lung more nearly to normal when the procedure is terminated. This decision should be based largely upon the physician's interpretation of the existing disease. This is determined essentially from X-ray studies, serial if available, plus certain clinical and laboratory procedures. There are many so called collapse procedures available. Pneumoperitoneum is one of these procedures which is useful in the control of certain types of pulmonary tuberculosis, and in certain instances is the only one which can be used in the individual patient.

There is a wide diversity of competent medical opinion regarding the use of any kind of collapse therapy with certain kinds of pulmonary tuberculosis. This should not be a matter of opinion but a matter of fact. Careful follow-up studies over a sufficient period of time, including comparable lesions treated by different means, will, in the long run, give us the necessary facts. In the meantime astute clinical judgment based upon wide experience and close contact with the individual patient is likely to be the best guide. In general, collapse therapy is receiving a wider application in less extensive types of lesions than was the case some years ago. (A more inclusive term than collapse therapy must needs be found if the present trend of "removal therapy" continues.)

Therapeutic pneumoperitoneum is one important method that is available to relax pulmonary tissue, allowing for partial splinting of the diseased portion of the lung to promote its healing. It appears that this is brought about by a reduction of the air content of the diseased area compared to the surrounding lung. This is readily demonstrated under the fluoroscope where the motion of the lung under pneumoperitoneum can be easily observed. It is not demonstrable upon X-ray films.

The use of pneumoperitoneum is generally not well understood by phthisiologists. There is a fear of putting a needle into the abdominal cavity, which, as we have shown above, is ill-founded. There is a further fear of complications, particularly the development of fluid, which we, and others, can demonstrate is not of sufficient moment to act in any way as a bar towards using the procedure. There is a lack of understanding of the necessity for frequent refills to keep the diaphragms at a properly elevated level. Too much attention is paid to manometric readings rather than to accomplishing the mechanical effect of adequate elevation of the diaphragm. This is a little difficult for one used to doing pneumothorax, but one must realize that the mechanics of the abdomen are quite different from that of the chest and that manometric readings of intra-abdominal pressure are of but minimal value in the control of this type of collapse.

Fluoroscopic control is the really important method in achieving adequate results.

We know of no instance where therapeutic pneumoperitoneum has been used adequately on enough patients over a sufficient period of time and the procedure not considered to have value. We know of a number of instances, however, where but a handful of patients have been inadequately treated and the procedure then considered to be without merit.

The length of time that pneumoperitoneum should be continued, as in the much longer experience with pneumothorax, is still not a settled question. In final analysis, it will depend upon following enough patients whose pneumoperitoneum has been voluntarily discontinued over a sufficient period of time to establish suitable criteria. It seems to us that 5 years is the optimal period of time to maintain pneumoperitoneum. This should be dated, however, not from the time the pneumoperitoneum was induced, but from the time it became effective; that is, sputum absent or negative by concentration, and cavities, if any, closed by X-ray. It may be that further experience will have us start the date of adequate collapse from the time that multiple stomach washes are negative to culture or guinea pig inoculation. Some method other than that of stomach wash for obtaining tubercle bacilli in the absence of sputum, such as bronchial washing, may be used, but that has not as yet received general acceptance.

It is interesting to see how extensive an involvement can at times be controlled by the use of pneumoperitoneum, and largely resolve. Of course, any one such case may be matched with results obtained from bed rest alone, but our figures give us a decided percentage in favor of the use of pneumoperitoneum in these cases against the most complete type of bed rest obtainable under the most favorable of institutional and other circumstances.

Cavitation is known to be a serious problem in pulmonary tuberculosis, and if not closed, to be associated with poor long-time results. Interestingly enough, there are other complications that are of great, or greater, importance in that they are less successfully controlled than cavity itself. In this series these were acute and massive bilateral caseous pneumonic lesions, and clinically diagnosable tuberculous tracheo-bronchitis. Tuberculous tracheo-bronchitis is the complication we have been able to cope with least successfully. This study, of course, antedates the use of promine and streptomycin which at the moment give evidence of improving the results.

In 1937, when we were feeling our way along in the use of pneumoperitoneum, we were so treating only the moribund and those patients with rather extensive bilateral lesions, those patients in whom pneumothorax had been proven impossible, and those in whom more rise in the diaphragm following a phrenic operation was thought desirable. As our experience increased, we gradually enlarged our indications in one direction to include the treatment of less extensive pulmonary disease, and retracted in the opposite direction, in the treatment of moribund patients and by the less frequent use of phrenic nerve operations. Based on the results as shown in this paper, there was a gradual transition to our present day indications for pneumoperitoneum therapy.

Our present indications for pneumoperitoneum therapy may be best shown in groups as follows:

A. According to the extent and type of disease, we would use pneumoperitoneum:

1. In minimal lesions, especially the acute exudative. These have been discussed in several places in the paper, and we will only point out here that our results have been excellent, recurrences rare, and the period of complete bed rest before beginning our graduated work-up regimen is usually only two months.
2. In moderately advanced lesions, without cavitation. Because the results warrant it, because complications are infrequent and not serious (particularly the absence of non-expansile lung as seen with pneumothorax), and because one can always change to a more radical collapse procedure should the need occur, we have gradually extended our indications to include more and more cavities in the less acute type of pulmonary tuberculosis. With the larger cavities, and especially the more acute lesions in the young age group, pneumothorax is still the procedure of choice.
3. With far advanced lesions, too extensive for other active collapse therapy, or where the patient's respiratory reserve precludes pneumothorax, we use pneumoperitoneum with the reasonable expectancy that one side will clear enough so that a unilateral pneumothorax or thoracoplasty may be done at a later date. Rather than rely upon bed rest alone, we would use pneumoperitoneum.

Pneumoperitoneum is especially useful in controlling exudative lesions prior to thoracoplasty when the indications for surgery are present but there is too extensive active tuberculosis on the contralateral side, or where the exudative lesions on the ipsilateral side are too extensive for thoracoplasty.

In the old age group (51 to 72 years) in the presence of emphysema and lessened respiratory reserve where pneumothorax may be considered somewhat hazardous, therapeutic pneumoperitoneum is a worth while procedure.

We still attempt pneumothorax in many cases which seem suitable, but it is in this group that pneumothorax is so often found impossible or inadequate, and where the risk of complications is great.

4. With tuberculous pneumonia, especially in several recent cases, we have had some good results with pneumoperitoneum. The lesion has become productive and thoracoplasty has effected the final cure.
- B. Where collapse therapy is thought advisable and other collapse procedures have been found impossible or inadequate, we use pneumoperitoneum as the next step in the collapse therapy program. This is especially true following pneumothorax failure, as we consider bed rest alone or a phrenic nerve operation inadequate if we have decided that collapse therapy was advisable. As a corollary, where pneumothorax is lost for any reason after

the lesion is arrested but before the collapse has been maintained for a sufficient period of time, immediate pneumoperitoneum continued to the time of optimum collapse gives good long-time results. In the control of postthoracoplasty spread of pulmonary tuberculosis, we have found pneumoperitoneum helpful.

C. In the following complications of pulmonary tuberculosis, we would use pneumoperitoneum:

1. With a clinically significant tuberculous tracheo-bronchitis. We feel that pneumothorax is contra-indicated when this complication is present, and although in this group the results with pneumoperitoneum are not as good as with other groups reviewed in this study, the percentage of good results in minimal and moderately advanced cases is sufficient to justify its continued use.
2. With pleurisy with effusion complicating pulmonary tuberculosis. Rather than replace the fluid with air to continue as a pneumothorax collapse (with the very high percentage of non-expansile lungs in this group), we now usually use pneumoperitoneum; certainly so, for the less extensive lesions. The results have been much better than with the six months bed rest alone we use in simple primary pleurisy with effusion where no parenchymal lesion was demonstrable.

The contra-indications are few, as follows:

1. Heart failure, and right heart failure (cor pulmonale); or
2. Moribund patients; extreme toxicity; or
3. Pregnancy; or
4. Large abdominal tumor.

#### CONCLUSIONS

The purpose of pneumoperitoneum is to achieve an adequate mechanical rise of the diaphragm, thus reducing the pulmonary volume and limiting the motion of the diaphragm with ordinary respiration. To be maintained, large weekly refills are necessary, guided by fluoroscopy. Manometric readings are of minimal value as a guide to extent of collapse. Phrenic nerve operations are usually not necessary.

Adequate pneumoperitoneum is a valuable collapse procedure in the treatment of pulmonary tuberculosis. Our immediate and long-time results amply confirm this. The period of complete bed rest is much shortened. The complications are not excessive and rarely serious.

The indications for pneumoperitoneum therapy have been greatly widened because of:

1. The good results obtained;
2. (As compared with bed rest alone)
  - a. the shortened period of complete bed rest, with the resultant economic saving to the patient;
  - b. the low exacerbation and recurrence rate;
  - c. the more rapid conversion of sputum;
  - d. the possibility of changing to a more radical collapse procedure should the need arise.

3. (As compared with pneumothorax)
  - a. the fact that it can be initiated in nearly all patients;
  - b. the fact that it is a completely reversible procedure and can be stopped at any time without danger of a non-expansile lung or pleural complications;
  - c. the possibility of reinitiating it should the need occur;
  - d. the relative lack of complications.

#### SUMMARY

Four hundred and seven consecutive case histories of pneumoperitoneum therapy were studied, and 382 of these analyzed according to results. Two hundred and eighteen patients (57 per cent) became arrested, and an additional 48 (13 per cent) were "definitely improved." The number of complications severe enough that pneumoperitoneum was discontinued varied, depending upon the view-point, from 23 to 28 (from under 6 per cent to about 7 per cent). The clinical status according to the duration of therapy is analyzed in detail, particularly the group of 41 patients in whom the therapy was voluntarily discontinued.

Analysis according to the extent of pulmonary disease showed that arrest occurred in 28 (82 per cent) of the 34 patients with minimal pulmonary tuberculosis, 107 (79 per cent) of the 135 moderately advanced, and 83 (39 per cent) of the 213 far advanced became arrested.

Of the 223 (58 per cent) patients with cavitation, 106 (47 per cent) became arrested and another 40 (18 per cent) were "definitely improved." Of the 171 patients with cavities of a total diameter of not more than 8 cms., 96 (56 per cent) became arrested; a sharp decline in the percentage of good results was noted with larger cavities. The position of the cavity within the lung, whether apical, in the mid-lung field or basal, made no statistically significant difference in the results obtained. In the 135 cases with moderately advanced disease, no marked difference was apparent between those with and without cavitation; 33 (73 per cent) of the 45 with cavitation became arrested and 74 (82 per cent) of the 90 without cavitation; in the 213 cases with far advanced disease, a marked difference was shown in favor of those with cavitation; 73 (41 per cent) of the 178 with cavitation became arrested in comparison with 10 (29 per cent) of the 35 without cavitation.

The results of pneumoperitoneum therapy in pulmonary tuberculosis complicated by tuberculous tracheobronchitis, pleurisy with effusion, and silicosis are discussed.

#### SUMARIO

#### *El Neumoperitoneo en el Tratamiento de La Tuberculosis Pulmonar: 407 Casos Consecutivos*

Después de repasar 407 historias clínicas consecutivas de neumoperitoneo terapéutico, 382 fueron analizadas con respecto al resultado. En 218 enfermos (57 por ciento) se presentó estacionamiento y en otros 48 (13 por ciento) "mejoría bien definida". El número de complicaciones de suficiente gravedad para imponer el abandono del neumoperitoneo varió, conforme al punto de vista, de

23 a 28 (de menos de 6 por ciento a 7 por ciento aproximadamente). Analizase a fondo el estado clínico según la duración de la terapéutica, en particular en el grupo de 41 enfermos en que se abandonó voluntariamente este tratamiento.

El análisis en relación con la difusión de la enfermedad reveló estacionamiento en 28 (82 por ciento) de los 34 enfermos con tuberculosis pulmonar mínima, en 107 (79 por ciento) de los 135 moderadamente avanzados y 83 (39 por ciento) de los muy avanzados.

De los 223 enfermos (58 por ciento) con cavernas, 106 (47 por ciento) se estacionaron y otros 40 (18 por ciento) "mejoraron bien definidamente." De los 171 con cavernas de un diámetro total de no más de 8 cms., 96 (56 por ciento) se estacionaron; cuando había cavernas mayores se notó una baja decidida en el porcentaje de buenos resultados. La posición de la caverna en el pulmón, ya en el vértice, el campo mesopulmonar o la base, no introdujo diferencias de importancia estadística en el resultado. En los 135 casos moderadamente avanzados, no hubo mayor diferencia entre los que tenían y no tenían cavernas, estacionándose 33 (73 por ciento) de los 45 que tenían cavernas y 74 (82 por ciento) de los 90 que no las tenían. En los 213 muy avanzados sí hubo una diferencia decidida en pro de los que tenían cavernas, estacionándose 73 (41 por ciento) de los 178 con cavernas, comparado con 10 (29 por ciento) de los 35 que no las tenían.

También se discute el resultado del neumoperitoneo terapéutico en la tuberculosis pulmonar complicada con traqueobronquitis tuberculosa, pleuresía con derrame y silicosis.

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## EXTRAPLEURAL PNEUMOTHORAX

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When in 1935 and 1936 Graff and Schmidt demonstrated the feasibility of maintaining an extrapleural pneumothorax, the procedure was welcomed as a method of using this effective form of collapse without incurring the complications occasioned by paraffin and other foreign bodies. Within the next few years it was widely adopted and enthusiastically proclaimed. Equally suddenly the enthusiasm waned. It was discovered that air also was a foreign body and that creating and maintaining the space entailed difficulties and dangers which were not immediately apparent. In 1942 Churchill wrote an article in which he stated that the operation was unsurgical and that it should be abandoned. Most surgeons did abandon it and today its advocates are few and suspect.

At Edward Sanatorium it has been used continuously since 1938 and is still used, not because we any longer believe that it is as good an operation as thoracoplasty or that it should ever be used when thoracoplasty is practicable, but because we are convinced that there are many cases which need unilateral or bilateral surgical collapse which, either because of low vital capacity or bilateral disease, cannot be subjected to thoracoplasty.

The purpose of this paper is to report our entire experience with the operation and on the basis of this to formulate our present ideas concerning its technique and indications. When dealing with a disease as protean as tuberculosis there is difficulty in establishing categories of surgical indications. This perhaps explains why the literature reveals a broad selection of patients and contradictory indications for extrapleural pneumothorax.

In an attempt to contribute to a re-evaluation of the extrapleural operation, a review has been undertaken of 86 consecutive cases performed at the Edward Sanatorium between 1937 and 1945. Particular attention has been given to the condition of the patient on admission, the extent and type of the lesions, and the dynamics of his disease. The therapeutic results have been based upon several factors, namely: sputum reports, serial x-ray examinations, the present physical condition, and the working capacity of the patient.

In regard to sputum reports, a "negative sputum" means either the absence of sputum combined with continuing clinical arrest, or three negative concentrations. Gastric lavage and guinea pig inoculations are not done on patients who have undergone surgery and are in good clinical condition unless they are to be in the same household as infants and children. It is felt that in many instances gastric lavage and guinea pig inoculation and cultures are too delicate tests for the clinical handling of pulmonary tuberculosis. They confuse and worry the patient and do not alter one's management or advice.

After so short a time and on the basis of so small a series in which the operation was used for so many different reasons, it has been nearly impossible to evaluate

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it on the basis of the number of patients cured. For the purpose of this paper it must be assumed that a procedure which produces a collapse of diseased lung sufficient to close cavities and render sputum negative needs to be examined only on the basis of its immediate and late complications. Nevertheless, an attempt has been made to evaluate the operation on the number of patients cured. In order that this may have some meaning, cases have been classified into six groups, representing six types of possible indications. It would be of no value to include in the same category patients with limited unilateral disease on whom thoracoplasty could have been used, and those with extremely far advanced bilateral cavitation on whom the operation was used as a desperate last resort and admittedly with little success.

The cases have been grouped as follows:

**GROUP I. MODERATELY EXTENSIVE BILATERAL DISEASE WITH AND  
WITHOUT CAVITIES IN PATIENTS WHO WERE GOOD  
SURGICAL RISKS**

The majority of patients in this group had diffusely scattered fibrotic lesions above the third rib anteriorly on both sides. Cavities, if present, were small. The remainder had similar lesions in the same locality on one side with contralateral mid-lung field or lower lung field involvement. After a fair trial on bed rest, resolution or fibrosis was insufficient and cavity closure was incomplete on the side elected for surgery. The exudative phase of the disease had subsided, and pneumothorax was either impossible or inefficient (figure 1).

With the extrapleural collapse established on one side the following conditions were observed to exist on the contralateral side:

1. Extrapleural collapse was done when the extent and the nature of the disease was similar to the other side, or
2. Pneumothorax was successful in controlling the lesion (figure 2), or
3. Stabilization occurred on bed rest alone.

The results in these 33 patients were as follows:

	NO.	PER CENT
Tuberculosis arrested. . . . .	28	87.5
Still have active tuberculosis . . . . .	3	9.5
Died of tuberculosis . . . . .	1	3
Total . . . . .	32	100

Of the 28 with arrested tuberculosis, 25 are working full time and two are working part time. One, after working for four years, developed a putrid lung abscess in the opposite lung and is still incapacitated on this account. One died of carcinoma of the stomach six years after the operation.

Of the three with active tuberculosis, one, after making a good recovery, developed hyperplastic tuberculosis of the cecum. Following operation for this she had an extensive hematogenous spread throughout both lungs. Another

lost her space and has at present active chronic disease in both lungs. The third patient is in excellent general condition but still has a positive sputum from activity under the extrapleural collapse.

The one patient who died had severe upper lobe bronchial tuberculosis. After the operation she developed atelectasis of the lower lobe and later spread of the disease to the opposite lung.

In two patients it was necessary to perform thoracoplasty over the extrapleural in order to close the cavity.



FIG. 1

FIG. 2

FIG. 1. A case from Group I which included patients with moderately extensive bilateral disease and who were good surgical risks. In this group, cavities, if present, were small and pneumothorax was impossible on the side elected for surgery. Date: 4/26/40.

FIG. 2. Another case from Group I with satisfactory pneumothorax on one side. The left lung was partially re-expanded before the Extrapleural was done on the right. Date: 3/2/41.

#### GROUP II. EXTENSIVE BILATERAL DISEASE IN PATIENTS WHO WERE NOT GOOD SURGICAL RISKS

The disease was progressing during bed rest, or the patient's condition was deteriorating. The surgical contraindications were not yet absolute, i.e., no marked degenerative changes, respiratory reserve fair, and general condition fair. Nearly all of these patients had the typical picture of far advanced fibro-cavernous, or hematogenous tuberculosis with all lung fields involved. Pneumothorax was impossible. The greatest activity was in the upper lung fields on both sides. These comprised the salvage group where it was considered worth while to risk failure in order to stop a progressive disease (figure 3).

The results in the 35 patients in this group are as follows:

	NO.	PER CENT
Tuberculosis arrested.....	16	44.5
Now have active tuberculosis .....	7	19.5
Died of tuberculosis.....	13	36
Total.....	36	100



FIG. 3



FIG. 4

FIG. 3. A case from Group II. This group consisted of patients with extensive bilateral disease who were not good surgical risks. Date: 12-5-40.

FIG. 4. The patient shown in Figure three after five months bed rest. As with all forms of collapse, Extrapleural pneumothorax is most likely to succeed and be free of complications when the exudative phase has been permitted to subside. Date: 5-16-41.

Fourteen of the sixteen patients with arrested tuberculosis are working and two are not working. The two patients who are not working are in good condition but become dyspneic upon exertion.

Of the seven patients with active tuberculosis, five had unilateral and two had bilateral extrapleural collapse. Of the five with unilateral collapse, three have arrested disease under the extrapleural but have active lesions on the other side. The fourth patient had a thoracoplasty over the extrapleural and the fifth patient continued to have activity under the extrapleural. Two of these patients had been discharged with arrested tuberculosis only to have reactivation three

and four years later. Of the two patients with bilateral extrapleural collapse, one continues to have activity on one side and the other continues to have activity on both sides.

Thirteen patients in this group died. In nine patients the extrapleurolysis failed to produce the desired results and the disease continued to progress. Of these nine patients, one lived three months after surgery, two lived eight months after surgery, and six lived from one to four years after surgery. Another patient had a fatal air embolism during a refill with air two months after surgery.

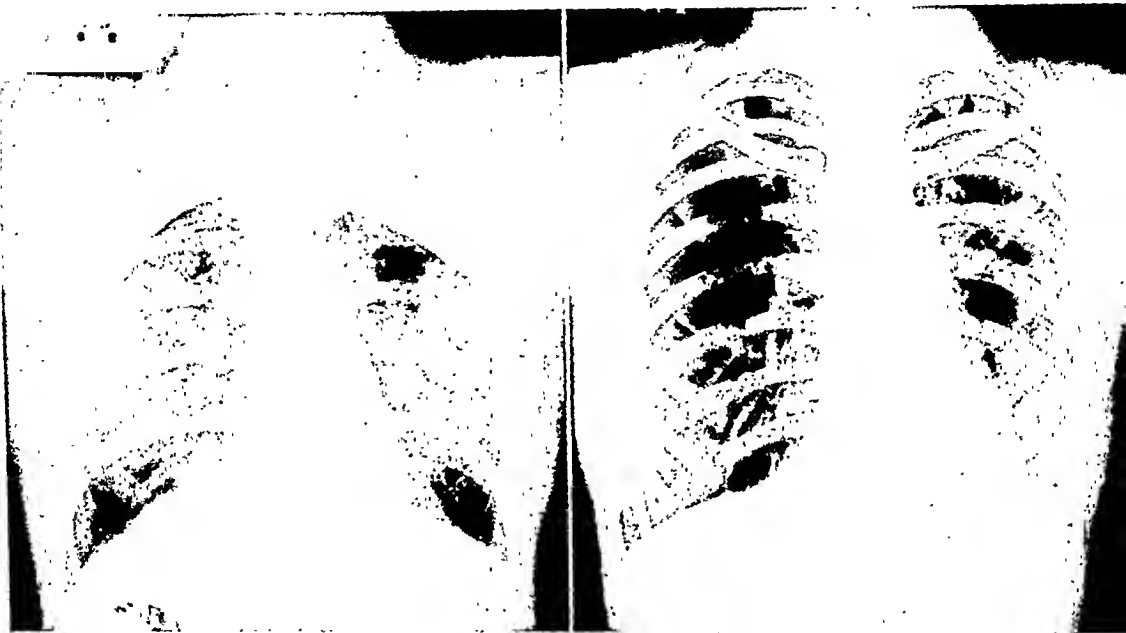


FIG. 5

FIG. 6

FIG. 5. The patient from Figure three with both spaces filled with oil. Date: 9/9/45.

FIG. 6. Group III consisted of patients with unilateral disease confined to the upper lobe. The Extrapleural was done to compare results with thoracoplasty. In this patient the cavity was considered to be too large, too low, and too near the hilus to be suitable for an Extrapleural pneumothorax. Thoracoplasty was advised and refused. This case appeared after 1945 and was not included in this series.

In one patient an anterior stage thoracoplasty was done to obliterate the extrapleural space. The patient died on the second post-operative day following a blood transfusion reaction. This occurred five years after the extrapleurolysis. One patient developed an esophageal-extrapleural fistula one month after the operation and died thirteen months later. It seems probable that it was consequent upon trauma to the esophageal wall at operation. When another patient, who had had recurrent symptoms suggestive of cholecystitis prior to the extrapleural pneumothorax, continued to have the same symptoms of increasing severity, it was decided to do a laparotomy. This was done six months after the extrapleural operation and at this time the sputum was negative and cavity

closure apparent. The exploration revealed miliary tuberculosis of the liver and the patient died several days after surgery.

Two patients in this group had thoracoplasty. One had a left lower lobectomy for bronchiectasis and later developed bilateral tuberculosis. An extrapleural was done on the left, but since it did not completely control the lesion, it was converted to a thoracoplasty after the contralateral lesion cleared. The other patient had a local thoracoplasty to obliterate a small space that remained after the extrapleural was permitted to reexpand. This patient's tuberculosis was arrested.

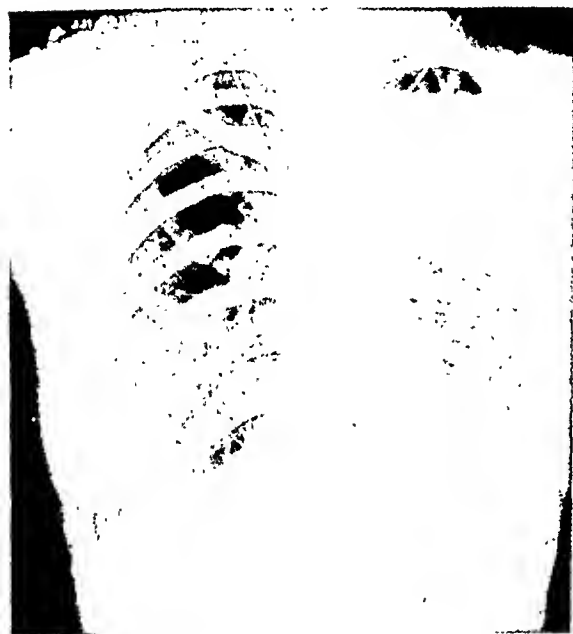


FIG. 7



FIG. 8

FIG. 7. The same patient shown in the preceding figure. The cavity is still open under the extrapleural space. This cavity closed after a three stage thoracoplasty. Date: 5/13/46.

FIG. 8. Group IV included patients with unilateral or bilateral disease with apical cavity held open by adhesions and contraselective basal collapse. The extrapleural space was combined with the intrapleural space. Date: 6/11/40.

### GROUP III. ALTERNATIVE TO THORACOPLASTY (FIGURE 6)

In this group the pathology was unilateral and confined to the upper lobe. No large cavities were present. Extrapleural collapse was done to compare the results with those of thoracoplasty. Patients with unilateral disease refusing thoracoplasty were included in this group.

Of the eight patients in Group III, all have arrested tuberculosis, are working full time, have negative sputa, and apparent cavity closure. There were two conversions to thoracoplasty in this group because of resistant tuberculous infection in the extrapleural space.

GROUP IV. UNILATERAL OR BILATERAL DISEASE WITH APICAL CAVITY HELD OPEN BY ADHESIONS. CONTRASELECTIVE BASAL COLLAPSE. EXTRAPLEURAL COMBINED WITH THE INTRAPLEURAL PNEUMOTHORAX (FIGURE 8)

Of the four patients in this group three are working full time and one is dead. The three patients who are working all have negative sputa and cavity closure but each had to have thoracoplasty because the combined operation failed to close the cavity. This procedure was apparently successful in controlling the lesion in the patient who died but later a cavity re-appeared in the opposite



FIG. 9

FIG. 10

FIG. 9. Patients in Group V had had a previous thoracoplasty on one side. On the other side, there was an apical and subclavicular infiltrate with cavity, and pneumothorax was impossible. Date: 8/5/42.

FIG. 10. The patients in Group VI had unilateral disease with a giant apical cavity. The Extrapleural was done to diminish the size of the cavity prior to thoracoplasty. In this patient, the giant cavity was merely pushed downward and not reduced in size. Date: 8/21/42.

apex. A paraffin plomb to compress this cavity was performed October 1945, two years after the extrapleural. He improved and was up and about at home but still had a slightly positive sputum. In August 1946 he had a severe hemorrhage with spread into the lower lobes. He died of anoxemia.

GROUP V. PREVIOUS THORACOPLASTY ON ONE SIDE. ON THE OTHER SIDE, APICAL AND SUBCLAVICULAR INFILTRATE WITH CAVITY. PNEUMOTHORAX IMPOSSIBLE (FIGURE 9)

The three patients in this group have arrested tuberculosis. Two are working, but the other is not working because of dyspnea upon exertion.

## GROUP VI. PREPARATION FOR THORACOPLASTY (FIGURE 10)

These patients had unilateral disease but each had a giant cavity in apex. An extrapleural was done in order to diminish the size of the cavity prior to thoracoplasty. There were three patients in this group all of whom have arrested tuberculosis and are working. Although thoracoplasty was intended for all patients in this group, it was necessary in only two. The third patient was spared from thoracoplasty because the cavity closed following the extrapleural.

The combined results in this series are as follows:

	NUMBER	PER CENT DISTRIBUTION
Number of patients.....	86	
Tuberculosis arrested.....	61	71
Tuberculosis still active.....	10	12
Died of tuberculosis.....	15	17
Total.....	86	100
Extrapleural operations.....	96	
Extrapleural collapse—effective.....	67	70
Extrapleural collapse—ineffective.....	29	30
Total.....	96	100
Cured by thoracoplasty.....	11	11
Early post-operative deaths attributed to surgery.....	0	0
Late post-operative deaths attributed to surgery.....	3	3
Conversions to oleothorax.....	74	76

\* Ten bilateral.

## COMPLICATIONS

The operation of extrapleural pneumothorax is difficult to perform and the handling and maintenance of the space in the early operative period requires skill and experience. As long as the space exists it is subject to complications. Most of the difficulties occurred in the early years when the indications for and the limitations of the operation were not well understood, and when the technique of creating and handling the space was being developed.

The early complications which have been encountered are:

1. The formation of blood clot in the extrapleural space—6 patients.
2. Production of intrapleural pneumothorax below the space—1 patient.
3. Spread into the same or opposite lung—1 patient.
4. Injury to the esophagus—1 patient.
5. Escape of air through imperfect closure of the space—2 patients.

*Blood Clot in the Extrapleural Space*

In spite of care at the end of the operation in controlling oozing from the walls of the space and in spite of filling the space with salt solution, some postoperative bleeding always occurs; occasionally this is sufficient to cause blood clots. When this occurs aspiration of the fluid and replacement of air is difficult or impossible. Trouble starts immediately. The temperature remains elevated, the lung tends to reexpand and in nearly every case infection eventually develops. The condition is suggested by difficulty encountered in aspirating the fluid and by persistence of fever. It can be recognized definitely on the x-ray which usually shows



FIG. 11. Irregular shadows above a fluid level suggest clot formation. The space should be immediately re-opened and the clot evacuated. Date: 7/3/42.

irregular shadows of the clot rising above the level of the residual fluid (figure 11). In the early cases this complication was often not diagnosed and, when it was, an attempt was made to continue the pneumothorax without removing the clot. In these cases low-grade fever persisted, the space gradually became inadequate and infected and, in one case, bronchial fistula developed. Today the condition is anticipated. If present, it is recognized early, and at the end of the first week the space is reopened and the clot removed.

*Production of Intrapleural Pneumothorax Below the Extrapleural*

Although extrapleural pneumothorax is rarely performed until intrapleural pneumothorax has been tried and found impossible or ineffective on account of adhesions, occasionally these adhesions are not complete. In such cases, in



performing the operation, the parietal pleura may be torn and an intrapleural pneumothorax, connected with the extrapleural space, is created. When this happens the extrapleural space is difficult to maintain, and some reduction in the degree of collapse usually develops. In our experience, however, the complication has never been insurmountable and in every instance the opening between the two spaces has eventually closed and the air in the pleural cavity has been absorbed. This has been accomplished by discontinuing refills until the lung had partially reexpanded and then restarting them and redeveloping the extrapleural space. In every instance a satisfactory collapse has been obtained.

#### *Escape of Air through an Imperfectly Closed Incision in the Rib Bed*

In many cases in the first day or days following the operation a small amount of air escapes into the tissues through the incision in the rib bed. Usually this is slight and unimportant. Occasionally it is sufficient to render difficult the maintenance of the space. If refills are given twice a day the openings will usually close before obliteration occurs. This complication also will be discussed under the heading of technique.

#### *Injury to the Esophagus*

This complication will be discussed under the heading of technique.

#### *Late Complications*

Those that have been encountered in this series are:

1. Infection in the extrapleural space.
  - a. Serous effusion—1 patient
  - b. Tuberculous empyema—2 patients.
  - c. Mixed infection empyema—9 patients.
2. Loss of space—2 patients.
3. Air embolism—1 patient.
4. Bronchial fistula—2 patients.

Infection in the extrapleural space with accumulation of serous or purulent fluid may occur either early or late. In this series there have been no instances of early primary non-tuberculous infection of the wound and the space. In two cases operated upon in the same week in 1943, a factory error in the preparation of the catgut with which the rib bed was closed led to acute effusion in the space and breaking down of the incision in the rib bed. This occurred two weeks after the operation and a week after the temperature had become normal. Both incisions had to be reopened and resutured. In both cases the catgut had disintegrated and the tissues about it were white and devitalized as if they had been cauterized with carbolic acid. In both instances the effusions were overcome by aspiration and irrigation, and both patients are now well.

Occasionally immediately after the operation, serous fluid continues to form in the extrapleural space. This is accompanied by fever and is probably tuberculous in origin. Repeated aspiration and replacement of air permit it to run its course. The infection eventually subsides and the fluid ceases to form.

In all save a very few of the cases the extrapleural space has eventually been filled with oil. For this reason most of our experience has been with effusions which develop under the oil. These may occur immediately from irritation, or months or years later, from tuberculous or non-tuberculous infection.

In an occasional case there is an immediate reaction to the oil as a foreign body. The temperature rises and serous fluid forms. This reaction is transient and subsides in a few days. Aspiration of the fluid may be necessary.

At any time, even years after the operation, tuberculous or non-tuberculous infection may develop in the extrapleural space. In these cases fever develops, there is pain in the area, and the x-ray reveals expansion of the space and fluid beneath the oil. Although it has not occurred in this series, one can assume that this increase in pressure threatens the development of a bronchial fistula, and that for this reason aspiration is immediately indicated. The condition, whether the fluid is serous or tuberculous or non-tuberculous pus, is also an indication for removal of all the fluid and oil and reconversion to a pneumothorax. This must then be washed out from three to seven times a week with 1-3300 azochloramid solution. If pyogenic organisms are present penicillin should be instilled at the end of each irrigation. Under the treatment the fever will rapidly subside and eventually the fluid will cease to form. If one wishes to maintain the collapse it is necessary to maintain the pressure in the intrapleural space by injecting air at the end of each aspiration. If, on the other hand, there is reason to believe that the tuberculosis, for which the collapse was instituted, has become arrested, an attempt should be made to reexpand the lung. This can sometimes be accomplished completely and often to such an extent that only a small space filled with clear fluid persists.

In summary one can say that while complications within the extrapleural space are relatively common and may occur either early or very late, they are bothersome rather than serious and can usually be met and overcome. They make the operation less desirable than thoracoplasty but they by no means contraindicate it in cases where thoracoplasty itself is contraindicated.

#### *Loss of Space*

Unless the space is very carefully watched and the pressure within it regularly raised each week to at least +20 cm. of water, it will gradually obliterate. Every case which we operated upon and then sent elsewhere for refills, and some of those treated in our own office, obliterated. In one instance this was the result of escape of air into the tissue through the needle hole and in another case the same cause almost resulted in reexpansion. So often did partial reexpansion occur and so constant was the threat, that we now convert every case into an oleothorax in the first few weeks after the operation.

#### *Air Embolism*

One case in this series died of air embolism immediately following a refill. In this case, which came early in the series, the air was forced in by a syringe. There is some reason to believe that excessive pressure rather than direct perforation of the lung, was the cause of the embolism.

### *Bronchial Fistula*

Broncho-extrapleural fistula is a rare complication. The two cases in this series were the result of errors in handling which have since been avoided. In one early case, a blood clot in the space was not removed, infection developed and eventually a fistula opened. In the other case the fistula followed an attempt to increase the collapse by forcing the oil into the space.

#### INDICATIONS

Extrapleural pneumothorax or oleothorax has the great advantages of providing a strictly local collapse of the upper lung which reduces the vital capacity very little, does not produce deformity, and is immediately and sometimes eventually reversible. It has the great disadvantage of creating a space which must be filled by a foreign body and which is subject to complications as long as it is maintained. Although these complications are rarely serious and practically never fatal, they are, in comparison with thoracoplasty, more important than the advantages. The operation should never be used when thoracoplasty is feasible. It should be used for collapse of disease in one or both apices when age, low vital capacity, or disease in the other lung contraindicate the preferable operation. It is most apt to be effective in closing small apical cavities and in controlling disease which is above the anterior part of the third rib. It is rarely effective for extremely large cavities or for those located below the first interspace or close to the hilus (figure 6 and 7). As with all other forms of collapse, it is most likely to be successful and free of complications when the disease has been rendered quiescent by a long period of bed rest (figure 4).

#### TECHNIQUE

A three-to-four-inch segment of the fourth rib is resected through an incision which extends from the spine to the angle of the scapula. Removal of a longer segment of rib is unnecessary for exposure and renders more difficult an air tight closure. Once the parietal pleura has been identified and a space developed by blind dissection with the finger, further dissection is carried out with a sponge dissector under direct vision aided by an Overholt lighted retractor.

The extent of the stripping and the size of the collapse obtained are of great importance and require experience and judgment. How far it is advisable to force matters in difficult cases and how far it is desirable to go in easy cases are questions upon which depends the success of the operation. One should aim to produce a collapse comparable to that afforded by a good apical thoracoplasty with a small apicolysis. The collapse should be slightly larger than one anticipates will be necessary. Too large a collapse invites complications. The early idea that this should approach that afforded by a good internal pneumothorax is not sound and accounts for many of the poor results which have tended to discredit the operation. It is neither necessary, safe nor desirable to free the lung entirely along the mediastinum. When this is done the collapse, which is chiefly downward, tends merely to displace the cavities and disease without closing or controlling them. It is necessary to free the lung from the apex of the thorax circumscribed by the first rib and for a short distance downward on the

mediastinum. It should be left attached to the mediastinum over the greater part of its surface. The collapse should be at an angle toward the upper mediastinum and the hilus. When this is done the cavity, rather than running away from the collapse, is held up where it can be compressed and closed (figure 5).

The handling of the space during the first week following surgery is important and sometimes difficult. At the end of the operation the space is left filled with normal salt solution. The next day the patient is made to sit on the edge of the bed and the fluid is aspirated through the second interspace anteriorly. It is replaced by air, and during the first week the pressure in the space is maintained at +20 cm. of water by daily refills. After this, weekly refills are usually sufficient. If more fluid forms this is aspirated until the space remains dry.

Difficulty encountered in removing all of the fluid and blood usually means that a clot has formed. In these cases one is able to aspirate only small amounts at a time and is unable to empty the space completely. This occurrence is a definite indication for reoperation to evacuate the clot.

After the space has been well established and fluid has ceased to reform, the air is gradually replaced by mineral oil. This is usually started a month or six weeks after the operation.

#### SUMMARY

Eighty-six cases of extrapleural pneumothorax and oleothorax performed over a seven-year-period have been divided into six groups in accordance with the pathological picture and the presenting problem.

An analysis of the results shows that in the earlier cases this operation was less successful and the complications more frequent and dangerous. This was due to uncertain indications, technical errors and improper handling of complications. These factors were chiefly responsible for creating a misrepresentation of this procedure. In the later cases the establishment of more definite indications with improvement in technique and aftercare provided good results with relatively few complications.

It should not be inferred from this that extrapleural pneumothorax is comparable to thoracoplasty. Thoracoplasty is a superior procedure and always more desirable where practicable. Extrapleural pneumothorax is resorted to only in cases presenting certain conditions in which thoracoplasty is not feasible.

In patients in whom the procedure was performed during the last three and four years the results have been comparable to those of thoracoplasty. The single drawback to the operation has proved to be the nuisance of minor complications in the space.

The indications, the technique, the incidence and treatment of complications have been discussed.

#### SUMARIO

##### *Neumotórax Extrapleural*

De acuerdo con el cuadro patológico y el problema planteado se dividió en seis grupos a 86 casos de neumotórax extrapleural y oleotórax, ejecutados durante un período de siete años.

El análisis del resultado revela que en los casos más antiguos la operación tuvo menos éxito y las complicaciones fueron más frecuentes y peligrosas, debiéndose esto a indicaciones inciertas, errores de técnica y atención inadecuada de las complicaciones. Estos factores constituyen la principal causa de que se haya creado una idea errónea de este procedimiento. En los últimos casos el establecimiento de indicaciones más precisas con el perfeccionamiento de la técnica y del cuidado subsiguiente ha dado buenos resultados con relativamente pocas complicaciones.

No cabe deducir de lo anterior que el neumotórax extrapleuraleal sea comparable a la toracoplastia. La toracoplastia representa un procedimiento superior y es siempre más conveniente cuando resulta factible. Al neumotórax extrapleuraleal sólo se le echa mano en los casos que presentan ciertas condiciones y en los que la toracoplastia no resulta factible.

En los enfermos en los que se ejecutó dicho procedimiento durante los últimos tres y cuatro años el resultado ha sido comparable al obtenido con la toracoplastia. El único inconveniente de la operación proviene del engorro de las complicaciones de orden menor que se presentan en el espacio afectado.

Discútense las indicaciones, la técnica, y la incidencia y el tratamiento de las complicaciones.

# BED-REST IN THROMBO-EMBOLIZATION IN TUBERCULOSIS<sup>1</sup>

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The pathogenesis of pulmonary infarction is a matter undergoing considerable discussion in present-day medical literature. The numerous factors involved in the production of thromboembolization have still to be evaluated, and this is true particularly with regard to bed rest. In view of the current interest in bed rest and because bed rest in the treatment of tuberculosis is fundamental and usually prolonged, it was thought that the population at Sea-View Hospital presented material suitable for a study of this particular facet of the problem of thromboembolization.

## MATERIAL AND RESULTS

The material studied was confined to a period of twelve years from June 1933 to August 1945. There were 24,263 admissions in this period. The number of deaths was 7,399, out of which 2,182 autopsies were obtained. The total number of cases with a diagnosis of pulmonary infarction was 30; of these, 22 were autopsied. They all had pulmonary tuberculosis. The youngest patient was 10 years of age; only 3 patients were over 50 years old. There were 7 cases in the second decade of life, 10 in the third, 5 in the fourth, 5 in the fifth, 1 in the sixth and 2 in the seventh.

In 13 of the 30 cases the diagnosis of pulmonary infarction was made clinically; of this group 5 cases came to post-mortem examination and the diagnosis was confirmed. The 17 undiagnosed cases were discovered at autopsy. Of the 13 cases diagnosed clinically, one patient is still alive; the source of embolization in this case was considered to be thrombophlebitis of the lower extremities.

The data pertaining to the pathogenesis of embolization in the seven fatal cases which did not have autopsies are as follows: three cases had thrombophlebitis of the lower extremities; the fourth was a case of recent coronary thrombosis with bundle branch block followed by two episodes of severe right lower chest pain, bloody expectoration, dyspnea and an x-ray picture indicative of pulmonary infarction. The second episode, in addition, had cerebral manifestations; the cause of death was ascribed to multiple infarctions. The fifth fatal case of pulmonary infarction occurred eleven hours after the third of a series of spine fusions. Speculation here revolved about the possibility of fat embolus as the agent of infarction.

The sixth and seventh fatalities occurred seventy-two hours and six days post-thoracoplasty respectively. The first of these two occurred unexpectedly in an individual progressing satisfactorily; the second fatality occurred in an individual with a concomitant cerebral involvement having the characteristics of and presumably due to an embolus.

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On the post-mortem table 22 cases were found to have pulmonary infarcts, an incidence among all autopsies of 1 per cent. The following is a summary of the pertinent findings in this group: As possible extrapulmonary etiologic factors of thrombophlebitis, tuberculous peritonitis was listed 6 times, tuberculosis of the pelvic organs was evident in seven cases, non-tuberculous pelvic disease was found in three cases. Bone tuberculosis was recorded six times. There were three cases of tuberculosis of the liver, 2 cases of renal tuberculosis and two of tuberculous laryngitis. Gangrene of the abdominal wall, fecal fistula, tuberculous pericarditis and retropharyngeal abscess were each listed once. Fistula of the chest wall was present in two cases. There were three cases of hematogenous dissemination, and in three instances no extrapulmonary lesions were found. Coronary thrombosis as a source of thromboembolization was present in 1 case.

It is apparent that in the majority of the cases circumstances were favorable for the establishment of focal thrombophlebitis with extension and subsequent embolization. The exact source of embolization escaped detection however, in 13 cases, and gross thromboses of the veins were recorded in only 9 cases.

Due to legal limitations which require special consent, it has never been the practice at Sea-View Hospital to routinely dissect out leg veins in performing autopsies. For this reason it is probable that the sources of the emboli are frequently overlooked when they occur in these vessels unless special attention is directed toward them by ante-mortem clinical observations. In most instances the pulmonary infarcts were incidental post-mortem findings. It may be significant that of the three cases with no demonstrable extrapulmonary lesions, one case (age 14) had thrombophlebitis of the lower extremities and one (age 40) had thrombophlebitis of both common iliac and hypogastric veins and an ante-mortem clot in the right auricle. In the third case (age 40) the source of embolization was not evident on post-mortem examination.

Among the nine cases in which gross venous thromboses were found, common iliac and femoral vein involvement were most frequently observed, having been noted three times each. The hypogastriacs were involved once, subclavian once, inferior vena cava once, in one case the right and left ventricles contained thrombi, and in one instance the thrombus was found in the right auricle. As evidenced in these overlapping figures, more than one source of embolization was frequently present in the same case.

Of the 13 cases diagnosed clinically, pulmonary infarction was felt definitely to be the cause of death in 8. Of the 22 cases which came to post-mortem 10 presented *fresh* pulmonary infarcts, mostly multiple. In only five cases, however, was the infarction considered the probable real cause of death. In the remaining five cases with *fresh* infarcts, cachexia and toxicity were considered as the primary cause of death in three instances, anesthesia in one instance, and in one case tuberculous bronchopneumonia. In 12 cases the pulmonary infarcts were found undergoing organization and apparently were not the primary cause of death. The majority of these patients died of terminal tuberculous bronchopneumonia, cachexia, toxicity and meningitis.

## DISCUSSION

Several years ago Coryllos and Auerbach (1) remarked on the relative rarity of pulmonary infarction in cases of pulmonary tuberculosis. More recently a similar observation was made by Peck and Willis (2). Indeed, 30 cases in a series of 24,263 admissions constitutes a strikingly small number in an institution where bed rest is a fundamental therapeutic procedure.

About 60 per cent of the patients at Sea-View Hospital spend at least 20 out of 24 hours in bed, while approximately 40 per cent are confined strictly to bed. Of the 7,399 patients who died in the course of the twelve year period, the majority were obviously confined to bed for long periods of time.

The post-mortem incidence of pulmonary infarctions in our series (1 per cent) is unusually low in comparison with various statistical studies which have revealed that embolism causes between 2 and 6.5 per cent of all deaths (3). This percentage, of course, does not include the incidence of non-fatal pulmonary infarctions.

We think that if bed rest were to play the important role in the pathogenesis of pulmonary infarction, the number of cases recorded in our group would have been greater. One must admit, however, that a certain number of pulmonary infarctions go unrecognized in an institution where chest pain, hemoptysis, dyspnea and attacks of faintness can be accounted for by the basic disease process. The shock syndrome is seldom, if ever, observed in pulmonary embolization with or without infarction in cases of pulmonary pathology. It was never recorded in our protocols. It seems that you cannot shock an already shocked organ. The reason, perhaps, lies in the fact that both the nerve and vascular patterns are so distorted in diseases of the chest, that alarming reflex responses are not readily elicited.

The role of bed-rest in the causation of thromboembolization is further diminished by specific pathophysiologic factors which exist in cases of pulmonary tuberculosis and are capable of producing infarction. Changes in the intrathoracic pressure occasioned by disturbed pleuropulmonary anatomy are conducive to stasis of the venous stream. The intrapulmonary vascular tree is also subject to anatomic and physiologic environmental influences conducive to intravascular clotting (4, 5). This consideration is born out by the fact that occasionally intravascular thrombi are found in branches of pulmonary arteries leading to infarcts in cases where no distant focus is found even on the post-mortem table.

Against the two factors assumingly favoring thrombo-embolization (bed rest and pleuropulmonary dynamics) there are three other factors which tend to diminish the incidence of intravascular thrombosis in an institution such as Sea-View: 1) the age of the patient; the population at Sea-View Hospital is predominantly of the younger age group; 2) the number of patients in cardiac failure; in this institution of 1500 beds the average number of such cases at any given time is 10; 3) in the material presented *thrombophlebitis* was the predominant pathologic finding in the veins studied and this entity is known to embolize less



readily than phlebothrombosis. The comparatively small number of pulmonary infarctions observed is apparently largely dictated by these three factors.

#### SUMMARY AND CONCLUSIONS

Thirty cases of pulmonary infarction were recorded at Sea-View Hospital in a period of twelve years during which there were 24,263 admissions (0.12 per cent). In 12 cases the pulmonary embolus proved fatal. In a series of 2,182 postmortem examinations performed in the same period of time there were 22 instances of pulmonary infarctions (1 per cent).

In evaluating the factors involved in the production of thrombo-embolization it becomes apparent that bed-rest is not a major factor in the pathogenesis of thrombo-embolization at Sea-View Hospital. The causes seem to be infection and possibly, to a certain extent, changes in the intrathoracic dynamics, as distinguished from the causes of pulmonary infarction in a general hospital where age, cardiovascular state of the patient and operative intervention assume a more dominant rôle.

#### SUMARIO Y CONCLUSIONES

##### *El Reposo en Cama en la Trombo-embolización en la Tuberculosis*

En un período de 12 años, que comprenden 24,263 ingresos, en el Hospital Sea View se registraron 30 casos de infarto pulmonar (0.12 por ciento). En 12 el émbolo pulmonar resultó letal. En una serie de 2,182 exámenes autópsicos ejecutados en el mismo período de tiempo, descubriéronse 22 casos (1 por ciento) de infarto pulmonar.

Al valorar los factores que intervienen en la producción de trombo-embolización, pónese de manifiesto que el reposo en cama no constituye un factor de mayor cuantía en la patogenia de dicho estado en el Hospital Sea View. Las causas parecen más bien ser: infección y posiblemente, hasta cierto punto, alteraciones de la dinámica intratorácica, en contraposición a las causas del infarto general en un hospital general en el que el papel dominante corresponde a la edad, el estado cardiovascular y la intervención cruenta.

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# TREATMENT WITH ANTIRETICULAR CYTOTOXIC SERUM IN PULMONARY TUBERCULOSIS<sup>1, 2</sup>

HERMAN R. NAYER

During the early phases of the development of the science of immunology, it was demonstrated that specific antibodies can be elicited in the animal body by injection of heterologous tissue extracts analogous to the production of antibodies by injection of the bacterial cell. A well known phenomenon of this type is the production of hemolysin specific for the red cells of one animal species by the serial injection of these red cells into an animal of another species. The antibodies developed in this manner, when brought together with the antigenic tissue cells, are usually "toxic" or destructive in their effect on these cells (cytotoxins); hemolysins and leucotoxins, produced by injection of white blood cells, are examples of this action.

In 1900, Metchnikoff (1) postulated that, while these tissue anti-sera were cytotoxic as generally used, much smaller doses would prove harmless and would, in fact, exert a stimulating effect on the specific tissue. In this manner, he proposed to strengthen the function of important tissue elements of the body. In pursuit of this hypothesis, Metchnikoff employed small doses of hemolytic serum in an attempt to increase the formation of erythrocytes. In 1924, Bogomolets (2) devised a method of controlling the titer and dosage of a cytotoxic serum by the use of the complement fixation reaction.

Subsequently, Bogomolets (2, 3) developed the concept of the "physiological system of the connective tissue". In addition to the reticulo-endothelial system, this system encompassed the elements and functions of the unformed connective tissue and all its derivatives such as osteoid tissue, fibrous connective tissue, macrophages and intercellular substance. This system was visualized as subserving various functions of major importance in the body economy: regulation of cellular nutrition and metabolism, healing of wounds, phagocytosis, production of antibodies, reaction of the body to new growths and regulation of internal secretions. Among other effects, stimulation of this system was, therefore, postulated to strengthen the resistance of the body to infection and to aid the processes of healing. In accord with the hypothesis of Metchnikoff, this stimulation could be brought about by the administration of small doses of serum containing cytotoxins specific for this tissue system. This material was named anti-reticular cytotoxic serum (ACS).

Anti-human reticular cytotoxic serum is prepared by intravenous injection of saline extracts of ground human cadaver spleen and bone marrow into animals, usually rabbits or goats. The antigen is most effective when obtained within ten hours after death. It is injected 5 to 6 times in increasing doses at intervals

<sup>1</sup> From the Division of Pulmonary Diseases, Montefiore Hospital, Gun Hill Road, New York 67, New York.

<sup>2</sup> The author is indebted to Dr. Harry Goldblatt, Los Angeles, California, for the ACS used in this study.

of 3 to 4 days. The peak of anti-body production is usually reached from the fourth to the seventh day after the last injection. Serum with a titer of 1-100 is considered acceptable for therapeutic use by the Russian investigators. In large doses, the serum is cytotoxic; in much smaller doses, it is supposed to exert a stimulating effect on the physiological system of the connective tissue. For a full discussion of the technical details of the preparation and preservation of ACS, articles by Russian and American workers should be consulted (4, 5).

Soviet workers (3, 6, 7) have reported favorable results with ACS in a wide variety of diseases, infectious, traumatic and neoplastic. In this country, Straus and co-workers (8) observed acceleration of healing of experimentally produced fractures in rabbits with small doses of homologous ACS and depression of healing with larger amounts. Stimulating and cytotoxic effects on a variety of tissue cultures, using specific anti-sera, have been reported by Pomerat and co-workers (9, 10, 11). Pomerat and Anigstein (12) identified the inhibitory factor of ACS within the globulin fraction.

There has been little reported clinical work with ACS in this country and none in clinical tuberculosis. Soviet workers (7) have suggested the possible value of the serum in tuberculosis giving few details. The histiocytic elements of the mesenchymal tissue play a most important role in the defense of the body against tuberculosis in both the exudative and productive phases. Arising from the reticulo-endothelial system, these histiocytes are of the greatest significance in walling off the disease and in the ultimate healing of the infection whether by resorption or fibrosis. Both the histiocytic elements and fibrous connective tissue are included in Bogomolets' connective tissue system. It would, therefore, appear that stimulation of this system might be expected to aid the body in resistance to and healing of tuberculosis.

A transient lymphocytosis in humans (3) and a marked lymphocytosis in dogs (13) have been reported following the use of stimulating doses of ACS. In dogs, the increase in lymphocytes was produced by doses of 0.04 cc./10 kg. A significant decrease in lymphocytes, a cytotoxic effect, was elicited by a dose of 5.4 cc./10 kg. An increase in the number of lymphocytes in the blood has been considered, by some investigators, as a favorable sign of increased resistance in tuberculosis. The production of a lymphocytosis would also be of theoretical value in enhancing resistance to the progression of tuberculosis.

#### METHODS AND MATERIAL

Ten patients with active pulmonary tuberculosis were selected for treatment with ACS (see table 1). Except in one instance, patients with predominantly acute exudative disease were not chosen in order to avoid any harmful effects of serum reactions. Patients considered suitable for collapse therapy at the time of this investigation were also excluded. One patient (case 2) had been subjected to a left five rib thoracoplasty one year before ACS therapy; he was treated primarily for active disease of the right lung. Case 10 presented a recent extensive caseous pneumonic spread; her outlook appeared hopeless with any other available form of therapy and it was deemed justified to test the effect of ACS.

At the onset of treatment, the general condition of seven patients could be classified as fair to good; the remaining three were in poor condition.

The material employed in all patients was lyophilized anti-human rabbit serum. On the day of the first injection, the serum was diluted with normal

TABLE 1

CASE	SEX	AGE	DURATION OF DISEASE	EXTENT OF DISEASE	TYPE OF DISEASE	MISCELLANEOUS DATA
			years			
1 (P. D.).....	F	33	3	far advanced bi-lateral	fibro-cavitary	symptoms of in-testinal tbc.
2 (L. K.).....	M	32	5	moderately ad-vanced bilat-eral	fibro-cavitary	left 5 rib thoroco-plasty, May 1946
3 (W. G.).....	M	26	10	far advanced bi-lateral	fibro-cavitary	laryngeal disease
4 (G. Z.).....	F	40	11	far advanced bi-lateral	fibro-cavitary	
5 (C. T.).....	F	33	1	far advanced bi-lateral	fibro-cavitary	bronchial tbc., left lower lobe
6 (C. F.).....	F	30	9	far advanced bi-lateral	fibro-cavitary	left oleothorax 1942; quiescent laryngeal dis-ease
7 (D. Y.).....	F	27	11	far advanced bi-lateral	fibro-cavitary	bilateral aban-doned pneumo-thorax
8 (R. P.).....	F	27	5	moderately ad-vanced bilat-eral	fibro-cavitary	
9 (F. P.).....	F	42	15	far advanced bi-lateral	fibro-cavitary	
10 (M. G.).....	F	48	3	far advanced bi-lateral	caseous pneumo-nia left lung; fibro-cavitary right upper lobe	critically ill

saline to make a ten per cent solution. A treatment series consisted of three subcutaneous injections of the diluted serum at 72 hour intervals as follows:

1st day..... 0.5 cc.  
 4th day..... 1.0 cc.  
 7th day..... 1.5 cc.

The diluted serum was kept in the refrigerator and was discarded after the third injection. The original intention was to give all patients two series at intervals of six weeks. However, this could be carried out in six patients; four received one series only for varying reasons (cf. below).

The dosage schedule was in accord with the recommendations of Dr. Harry Goldblatt and is based on the Russian use of the serum. It was also felt that treatment in two series over a period of approximately two months, with a further follow-up period, would be long enough to reasonably evaluate any specific effects.

X-ray and sputum studies were carried out at frequent intervals. The following laboratory procedures were carried out before and after each series: blood count, blood urea nitrogen determination, urinalysis, cephalin flocculation and thymol turbidity tests for liver function; these were all within normal limits at the beginning of treatment.

#### SIDE REACTIONS

A few patients manifested transient febrile reactions during treatment; more significant febrile reactions are discussed below. Several patients developed skin sensitivity to the rabbit serum after the first series; during the second series, the serum was administered to these in divided doses with no significant reaction except some local discomfort and mild generalized pruritus which was controlled with pyribenzamine. The patient with extensive caseous pneumonic disease received two series with no significant local or general reaction.

#### RESULTS

Up to the time of this report, x-ray and clinical follow-up has been carried on for more than two months after the second series, approximately four months after the first series. No beneficial results which could be ascribed to ACS were observed in this group. One patient (case 8) did show some resorption of pulmonary infiltrations in one lung, accompanied by gain of weight and general clinical improvement, following the first series. This improvement, however, had begun before serotherapy was instituted and did not appear to be accelerated by treatment. The remainder showed either no objective change or progression of their disease. Subjectively, a few patients volunteered a feeling of general improvement for a short period after the injections; this was difficult to evaluate and the immediate psychological effect of any "new" treatment in tuberculosis is often observed.

Blood urea nitrogen, urinalysis, cephalin flocculation and thymol turbidity tests all remained within normal range during and after treatment. Sputum remained positive throughout. Blood counts revealed no significant lymphocytic reaction; some of these counts were not carried out until several days after treatment and a transient alteration may have been missed. No significant changes were observed in any of the other cellular elements of the blood.

Three patients developed varying reactions during or after the first series which, in our opinion, made the administration of a second series hazardous. Case four developed fever up to 101° several hours after the third injection; this was accompanied by general malaise and returned to normal within one week. There were no changes in the pulmonary status of this patient. In case 6, examination of the larynx one month after serotherapy revealed some

progression of the laryngeal disease which had been present and stable before treatment. In case 7, fever of 103° developed two days after the second injection; this was accompanied by some redness and swelling at the injection site. By the following day, the temperature had dropped to 99.8° and the third dose was given without reaction. Chest x-ray taken on the same day revealed an increase in size of infiltrations previously present in the left lower lobe; one month later, a small cavity was noted in this region. In this patient, a harmful focal reaction could be reasonably ascribed to the use of serum.

There was one postmortem examination in the treated group. Case 3, the fourth patient who received one series of the ACS, died one month after treatment. He had far advanced progressive disease before therapy and this progression continued unaltered after treatment. Autopsy revealed extensive pulmonary tuberculosis and intestinal ulceration with no unusual gross or histological findings.

#### SUMMARY

1. Ten patients with advanced progressive pulmonary tuberculosis were treated with antireticular cytotoxic serum.
2. During follow-up periods of four months, no beneficial effects were observed.
3. In one patient, a harmful focal effect could be ascribed to the use of the serum.

#### SUMARIO

##### *El Suero Citotóxico Antirreticular en la Tuberculosis Pulmonar*

1. Diez enfermos con tuberculosis pulmonar evolutiva avanzada fueron tratados con suero citotóxico antirreticular.
2. Durante un período de cuatro meses de observación subsiguiente no se observó efecto beneficioso.
3. En un enfermo, pudo imputarse al suero un efecto focal nocivo.

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## PLEURAL FAT PADS<sup>1</sup>

### A Cause of Thoracic Shadows

LEONARD C. EVANDER

The possible presence of fat pads in the parietal pleura appears to be a forgotten point in the differential diagnosis of thoracic shadows. We have either been negligent in our examination of the roentgenogram, or considered these pads to be of no consequence. Their occurrence, however, should be of interest to the radiologist and chest physician. A lack of understanding that fat deposits can cause pleural densities, may cause the density to be viewed as a pathological finding.

Comparatively little attention has been directed towards the subject of fat tissue. In the commonly used books on normal anatomy only the muscle and fascia relationships are considered. The anatomy of the inner thorax surface is briefly presented, and the occurrence of fatty deposits ignored. Gruber (1) found that the fat tissue often developed because of an inflammatory process, on areas of the pleura which macroscopically appeared thickened. Microscopically, there was a more or less developed layer of subpleural anthracotic pigment on the edge of the lung tissue, then a variable thick zone of fibrous tissue containing scanty blood vessels, and then joining with a thin zone of granulation tissue there was a strongly developed fat tissue. The fat appeared lobularly arranged within the pleura. Brandt (2) also believed that fatty tissue building, on the free lung pleura, can only occur in attendance with considerable and chronic inflammatory processes, such as a chronic adhesive pleuritis. Knutsson (3), in a discussion of the inner attending shadows of the pleura, mentions the occurrence of fatty deposits in the parietal pleura without any further consideration of their presence. Lauche (4) gives one of the most detailed textbook descriptions: "The parietal pleura often contains a rich amount of fatty tissue, which stands out over the surface in the shape of small, oblong beds and folds. The visceral pleura is usually fat free." Even this description affords us an incomplete picture of pleural fat pads.

Neugebauer (5), on the basis of numerous post-mortem examinations on normal organs (following accident or suicide), believes that one can very often find fatty deposits in the non-pathologically changed pleura. He presents a detailed picture of the size, form, arrangement, and topography of the deposits. The fat pads usually vary with nutritional status, but may be strongly developed even under average conditions or may be completely absent in young well-muscled males. Also in the newborn, there are, not infrequently, narrow gold-yellow streaks on the inner rib surfaces, representing the foundation of the pleural fat pads. Their insertion occurs only on the inner surface of the ribs and never in the intercostal space. If strongly developed, the pads can sink downward like an apron and cover the next deeper rib completely. In this fashion they can form

<sup>1</sup> From the Niagara Sanatorium, Lockport, New York.



a shingle roof-like covering of the inner rib surfaces, and only a spreading of the pads will reveal the individual layers. It has also been noted that the thorax can be divided into three zones, based on the arrangement of the fat. In the upper one-third of the thorax, third and fourth ribs, the fat ridges are seldom as strongly developed as in the lower portions. The pads on the third and fourth, and sometimes on the fifth rib, begin in the region of the angulus costarum and decrease in intensity as they extend ventrally to the posterior axillary line. In the middle third of the thorax, including the fifth, sixth, and seventh ribs, the pads extend to and sometimes reach beyond the anterior axillary line. The fat ridge of the eighth rib, often representing a transition to the lower third, extends only to the posterior axillary line. On the ninth and tenth ribs, in the lower thorax third, the pads barely reach the posterior axillary line and occasionally only the scapular line. It is in this portion of the chest that the shingle-like arrangement occurs most often. Though there are sometimes differences of one or two ribs, the pads generally follow the above outline. However, their dorsoventral course is not always continuous and often shows variations in density. The fat ridge may divide into pads and ridges, while in extreme cases there may be fat-free spots or only a narrow bridge-like streak joining the pads.

In 1927, Fleischner (6) reported that occasional, small, streaky, soft tissue shadows could be noted along the inner surface of the chest wall on the lateral x-ray. He considered them as part of a pathological process which he designated as "lamellar pleuritis". Herrnheiser (7), however, felt that these shadows were not always pathological, but could be caused by normal soft tissue such as subpleural connective tissue or fat masses. Also, it was not unusual to find these shadows symmetrically arranged in patients who never had shown clinical signs of pleurisy. Knutsson (3), in his roentgen-anatomical study on the same subject, stated that the accompanying shadow of the thoracic wall is formed by a muscle layer at the inner surface of the ribs. Furthermore, these muscles are normally seen only at the uppermost ribs on the lateral projection. The middle and lower ribs did not show any muscle layer overlying the inner surface. Therefore, the accompanying shadows, which were seen in the lateral projection of these regions, would have to be noted as pathological formations. Herrnheiser (7) disagreed also with this view, claiming that normal soft tissue could cause the accompanying shadows even in the middle and lower areas. Kubat (8) found that, on the upper ribs, the ridges extended to the anterior axillary line; that, at the lower ribs, they were restricted more to the posterior portions. The width and localization of the accompanying shadows coincided distinctly with the fat ridges. Those fat accumulations of 1 to 2 mm. did not produce any distinct accompanying shadow, but ridges of more than 2 mm. thickness could be seen either as segmented or continuous stripes. Where the fat ridge was strongly developed, Kubat noted that, on the lateral projection, the fat pad protrudes below the lower margin of the ribs with a complete or partial bridging over of the intercostal space. After these fat cushions were dissected, the accompanying shadows could not be produced. He also found that these shadows remain visible on the roentgenogram, even after collapse of the lung by pneumothorax.

The American literature does not offer much information concerning these fat pads. Wells (9) has comprehensively reviewed adipose tissue, but he makes no mention of its subpleural occurrence. Our interest in this matter resulted from the following case:

*Case I:* W. K.: 35 year, white male, was admitted to the Niagara Sanatorium, December 31, 1945, following a six week history of cough, expectoration, hoarseness and slight hemoptysis. Admission roentgenogram revealed bilateral mottled infiltration extending to the fourth anterior space on the right and third anterior space on the left. A 2 cm. sized cavity was present at the lower pole of the right hilum and a 1 cm. cavity in the left mid-field. Because of these findings, and sputum positive for tubercle bacilli, right pneumothorax was advised and attempted on January 7, 1946. The site selected was in the axillary line, slightly above nipple level. Since the manometer showed no fluctuation, this site was abandoned and another attempt made one interspace lower, also in the axillary line. The patient could now receive 300 cc. of air, with good readings. However, the cavity remained open, apparently due to the presence of adhesions. On February 27, a right pleuralysis was attempted. Following local infiltration of the third interspace in the mid-axillary line, it was found necessary to insert the novocain needle for about 2½ inches before striking the pneumothorax pocket. A check on the X-ray revealed some haziness at this region. The density, however, did not appear to be caused by the pectoral muscle, scapula or lung parenchyma. It was then decided to discontinue at this site. The fourth interspace was infiltrated and used for insertion of the thoracoscope. Over the third interspace, on the parietal chest wall, a loose somewhat pedunculated lipoma about 3 inches long and 1½ inches wide was described. Numerous string adhesions, a cord, and a long dense band were found, and severed. The patient's X-rays were now reviewed, with the diagnosis of lipoma in mind. It was noted that the previously mentioned area of haziness extended from the lateral one-third of the second anterior space downward and laterally, to beneath the peripheral portion of the fourth rib. The haziness appeared to be heavier along the lateral chest wall, becoming finer and more irregular towards its medial portion. Because of this finding, the literature on intrathoracic lipomas was checked. Heuer (10) had presented a case of intrathoracic lipoma and a report on the preceding literature. The tumors, previously reported, had ranged in size from a walnut to a filling of an entire thorax. According to their anatomic location, the cases had been divided into three groups. One group consisted of those lipomas which lie entirely within the thoracic cage. Heuer offered the X-ray as an aid to diagnosis. He had noted that a lipoma has a characteristic shadow; that there is a transparency of the edges when compared with the dense central portion. McCorkle, Koerth and Donaldson (11) advised noting the sensation produced when the needle is inserted into the chest wall. The insertion into a lipoma causes a sensation of penetrating into a buttery or boggy mass. Though we had no biopsy proof, our findings otherwise appeared to agree with a diagnosis of intrathoracic lipoma.

Because of continuing cavitation on the left side, the patient had a pneumothorax induced on this side. The roentgenogram of April 13 showed an area of haziness along the left chest wall, similar to that described on the right side. This finding served to complicate the picture. It was felt that a diagnosis of bilateral lipoma would be rather unusual, and should be withheld until thoracoscopy and biopsy could be done. No other diagnosis could be offered, however. On April 20, the patient began to show symptoms of meningeal irritation and spinal fluid, removed on three occasions, was typical of tuberculous meningitis. The patient's course was steadily downhill, with death on May 7.

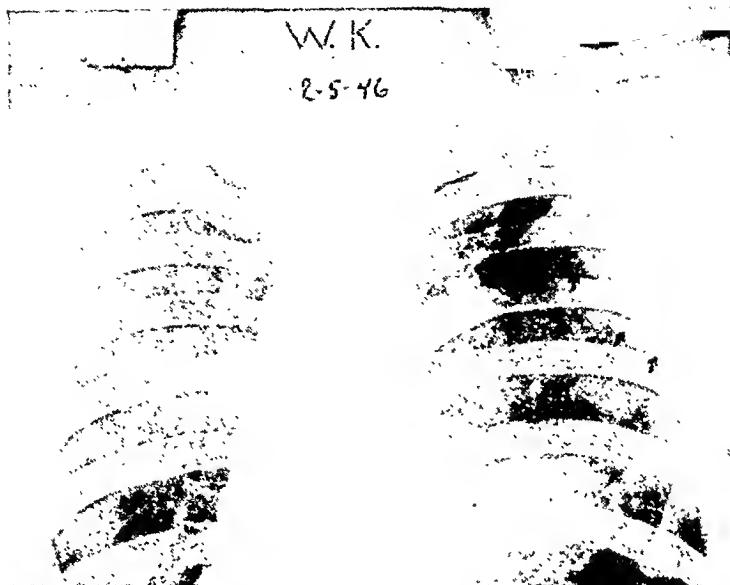


FIG. 1. Case I. (2-5-46.) This X-ray, taken prior to pleuralysis, shows the area of haziness along the right lateral chest wall. The density extends from the second anterior space to beneath the fourth anterior rib. At the time of thoracoscopy, this density was considered to be a pedunculated lipoma.

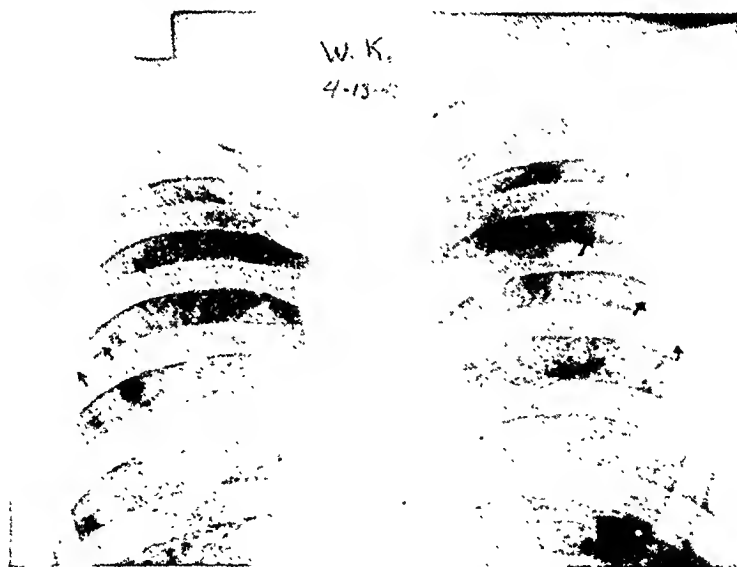


FIG. 2. Case I. (4-13-46.) The adhesions on the right side have been severed, and pneumothorax has been induced on the left side. There is an area of haziness along the left lateral chest wall, apparently identical with that on the right side.

Autopsy, done on the same day, revealed a very well developed white male, with musculature of distinctly athletic build. Fatty tissue was found to line both chest walls, in the same manner as described by Neugebauer (5). Also seen were several of the larger types of fat pads, as had been noted at thoracoscopy.

Two patients who also required pleuralysis afforded us the opportunity to check on preoperative X-ray findings by means of the thoracoscope.

*Case II:* W. F.: 32 year, white male, was first admitted to Niagara Sanatorium in May 1945, following hemoptysis. A left pneumothorax was induced because of lower lobe



FIG. 3. Case II. (4-7-47.) X-ray, taken prior to right pleuralysis, reveals areas of haziness along the right chest wall from the first to fourth anterior interspaces. Apparently identical areas are seen along the left lateral wall from the first to third anterior spaces (the fourth space being obscured by the marginal pneumothorax). One can note that the densities appear to extend from the lower margin of the posterior rib, and do not reach the upper margin of the next lower rib. Yellowish, fatty-appearing tissue was found during thoracoscopy on the right side.

cavity and positive sputum. The patient's sputum became negative, and he was discharged in January 1946. In November 1946, increased disease was noted in the right upper lobe, with the sputum again positive for acid-fast bacilli. He returned to the Sanatorium in January 1947, receiving right pneumothorax one week later. Right pleuralysis was advised because of adhesions, and performed on April 9. The preoperative X-ray

showed irregular, hazy areas extending from the first anterior space downward to the fourth anterior space along the lateral portion of the chest. Apparently identical appearing haziness was noted along the left chest wall, from the first to the third anterior spaces. With the roentgenological and autopsy findings of case I in mind, it was felt that these shadows represented pleural fat deposits. Following novocain infiltration, the thoracoscope was inserted in the third anterior space, in the right mid-axillary line. The electrode was inserted in the third anterior space, slightly medial to the mid-clavicular line. After the severance of an apical band, there was a marked drop of the apex and the interior of the cage could be well visualized. It was noted that within the third to sixth posterior interspaces, there were rounded, yellowish, fatty-appearing pads.

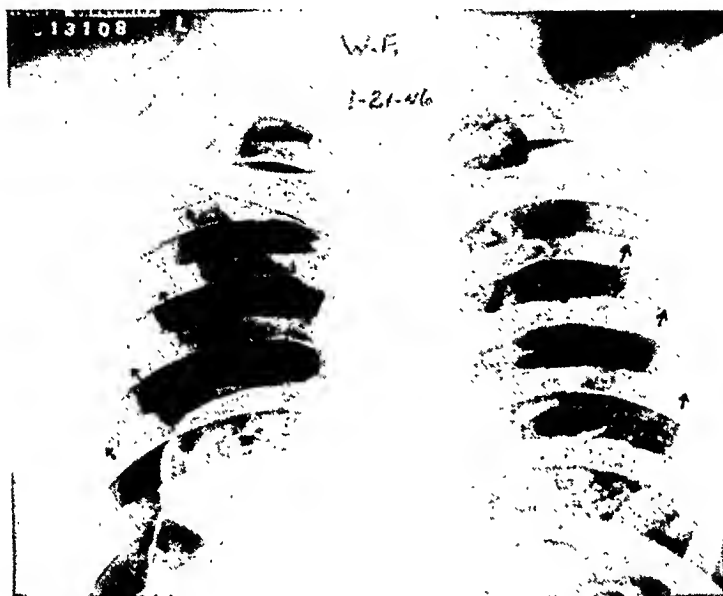


FIG. 4. Case I. (1-21-46.) Following a review of the patient's earlier X-rays, it was noted that areas of haziness had been present along the left lateral chest from the first to fourth anterior spaces. No attention had been paid to these areas. Even at this time the areas of increased density, better visualized after the induction of pneumothorax, can be seen along the right lateral wall.

As in the first case, the patient's previous X-rays were reviewed. Soft, hazy areas could be visualized along the peripheral portions of the left first to fourth anterior spaces. These shadows had been present during the course of left pneumothorax therapy but no attention had been paid to them. Now, even without thorascopic check of the left side, we feel that these shadows can be diagnosed as pleural fat pads.

*Case III:* F. R.: 50 year, white male, was admitted to Niagara Sanatorium on March 26, 1947. In 1918, the patient had pleurisy on the left side and was quite sick for about two months. An X-ray, about 1937, showed apparently healed disease. He had no complaints until three months prior to admission. At this time, he developed a productive cough, anorexia and weight loss. On admission, there was infiltration, with a suspicious area of cavitation, present in the left upper lobe; the sputum contained acid-fast bacilli. Pneumothorax was advised, but patient decided to try bed rest. After two months of

rest, without any improvement of the disease, he consented to pneumothorax therapy. Left pneumothorax was induced on 6-16-47, followed by a pleuralysis on 7-17-47. The thoracoscope was inserted in the third interspace in the left axillary line. As the thoracoscope was passed towards the apex, an overhanging mass, hanging down along the parietal pleura, was encountered. It was necessary to push the thoracoscope in for a considerable

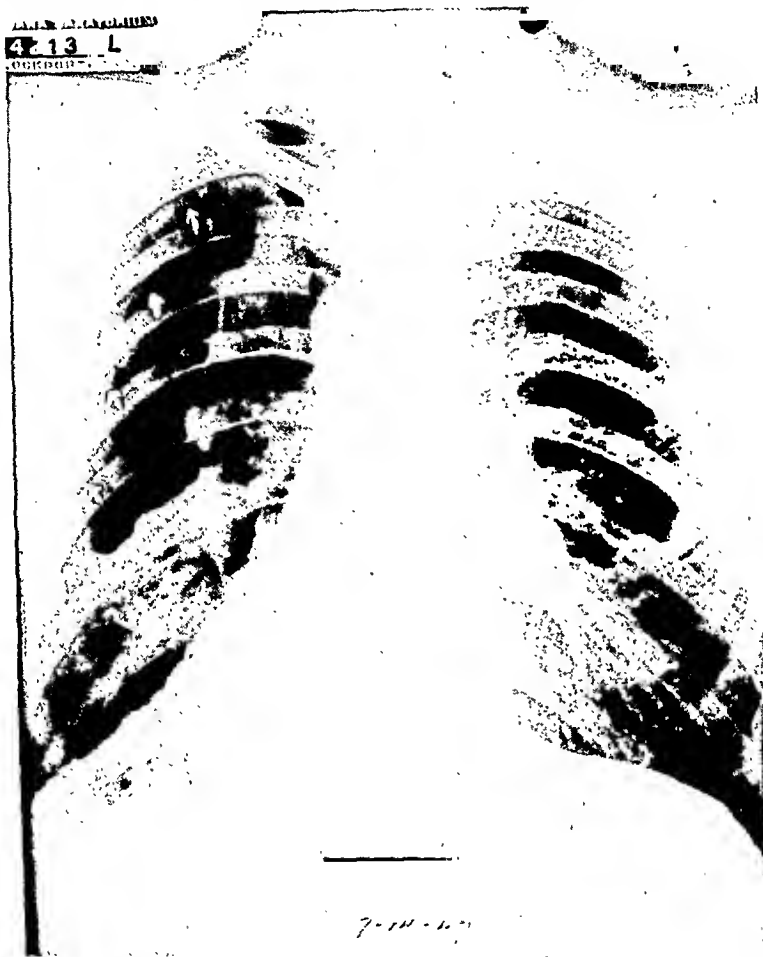


FIG. 5. Case III (7-14-47.) X-ray, taken prior to left pleuralysis, reveals areas of haziness along the left chest wall from the first to fourth anterior spaces. Here again, the densities apparently extend from the lower margin of a posterior rib and do not reach the upper margin of the next lower rib. This patient also appears to have an epicardial fat pad, with an obliteration of the left cardiophrenic angle.

distance, first pointing the scope downward and then elevating it, to get beyond this mass. After the adhesions at the apex had been severed, with a complete collapse of the upper lobe, the interior of the chest cage could be better visualized. Re-examination showed a large, pad-like area of yellowish, fatty tissue, extending approximately from the second to the fifth anterior spaces and between the axillary lines.

Here, too, the finding of fat pads had been anticipated. On the preoperative X-ray, it had been noted that there were areas of increased density along the left lateral wall from the first to the fourth anterior spaces.

## COMMENT

There does not appear to be any definite explanation that one can offer for the occurrence of these fat pads. If they are to be considered as storage fat, one must remember that the fat ridges may be absent or poorly developed even in people having a good nutritional condition. As has been mentioned, Gruber (1) and Brandt (2) observed fat in the pleura in adhesive pleuritis and explained the occurrence on the basis of a chronic inflammatory process of the pleura. In the first two cases, there was no evidence of intrapleural fluid during pneumothorax and no past history of pleurisy. Case III had had pleurisy, type unknown, almost thirty years ago. It has also been thought that, during a shrinking process of the lung, the present fatty tissue may develop and occupy the vacated space. Neugebauer (5), however, in his autopsy material never found this strong development in thickened pleura, which had been caused through a shrinking of the lung. One can only say that the fat pads of the pleura are analagous to the subserous fatty deposits of the other body cavities.

## SUMMARY

In the normal parietal pleura fatty cushionings of various stages of development may occur. The padding can be extensive, forming a roof-like covering on the inner surface of the ribs and act as a buffer for the pleura. These fat pads have been neglected in the anatomical literature, although they are of common occurrence and practical importance in roentgenological diagnosis. They may be observed both on postero-anterior and lateral films. Since they are not described in our standard books, these densities may erroneously be considered as pathological findings.

Based on the observations during thoracoscopy, we believe that the opinions of Neugebauer, Kubat and Herrnleiser, regarding the etiology of the pleuritic shadows, are correct. In the author's cases, the pleural densities could be seen on X-ray films during pneumothorax therapy, and the fatty deposits were seen through the thoracoscope. In the first case, the fat pad interfered with the induction of pneumothorax and the insertion of the thoracoscope. Lipoma was originally diagnosed, and not corrected until postmortem examination was done. A knowledge of these fatty deposits, however, made possible a correct preoperative diagnosis in the second and third cases. In patients with pneumothorax, with the lung collapsed away from the chest wall, these densities can be easily recognized on the roentgenogram. Physicians interested in diseases of the chest should remember pleural fat pads in differential diagnosis.

## SUMARIO

*Los Paquetes de Grasa Pleural: Causa de Sombras Tordcicas*

En la pleura parietal normal pueden presentarse paquetes de tejido adiposo en varios períodos de desarrollo. Esos cojines pueden ser bastante extensos, formando una especie de techo sobre la cara interna de las costillas y sirviendo de resguardo a la pleura. En la literatura anatómica se han pasado por alto esos

paquetes adiposos, aunque son frecuentes y revisten importancia práctica en el diagnóstico roentegenológico. Pueden ser observados en las películas tanto anteroposteriores como laterales. Como no las describen los libros de texto corrientes, esas sombras pueden ser consideradas erróneamente como hallazgos patológicos.

A juzgar por las observaciones realizadas durante la toracoscopia, parecen estar bien fundadas las opiniones expresadas por Neugebauer, Kubat y Herrnheiser acerca de la etiología de estas sombras pleurales. En los casos del A., podían observarse las sombras en las películas radiográficas durante la neumotoracoterapia y los depósitos adiposos fueron distinguidos a través del toracoscopio. En el primer caso, el paquete de grasa obstaculizó la inducción del neumotórax y la introducción del toracoscopio. El diagnóstico de lipoma formulado al principio no fué rectificado sino al hacer la autopsia. Sin embargo, el conocimiento de estos depósitos de tejido adiposo permitió hacer un diagnóstico preoperatorio acertado en el segundo y el tercer casos. En los enfermos con neumotórax, con el pulmón aplastado y alejado de la pared torácica, pueden reconocerse fácilmente estas sombras en la radiografía. Los médicos interesados en las afecciones del tórax deben recordar los depósitos adiposos en la pleura al hacer el diagnóstico diferencial.

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# EFFECT OF BENADRYL HYDROCHLORIDE<sup>1</sup> ON THE TUBERCULIN REACTION IN GUINEA PIGS

R. W. SARBER<sup>2</sup>

There has been considerable recently published evidence supporting the effectiveness of antihistamine agents in both allergic and non-allergic dermatoses and other skin manifestations in both man and laboratory animals (1-6). In the course of our work it became desirable to have evidence on the possible effect of antihistamine agents on the tuberculin reaction. Although there is some disagreement concerning the mechanics and classification of the various phases of tuberculo-immunity, we feel that specific tuberculo-allergy as manifested by the tuberculin skin reaction is a distinct entity (7).

Boquet (8) investigated the action of certain antihistamine compounds (2-diethylaminomethyl-1,4-benzodioxane hydrochloride (883 F); N-phenyl-N-benzyl-N',N'-dimethylethylenediamine hydrochloride (2339 R.P.);  $\beta$  thymoxyethyldiethylamine hydrochloride (929 F)) on the intradermal tuberculin reaction in guinea pigs and was unable to demonstrate any appreciable reduction in reaction intensity. However, it is to be noted that tuberculin tests were generally performed immediately after the administration of a single dose of antihistamine agent without evidence of an "adequate" drug level being reached or maintained throughout the time the tuberculin test was developing. Also, a 1:10 dilution of tuberculin (Old Tuberculin) was used for testing. Such a quantity of tuberculin, if of usual potency, will normally create an extremely strong reaction as compared to the usual testing doses of 1:100 or 1:1000 dilutions (1:1000 and 1:10,000 tests). On the other hand, Breton (9), in attempting to elucidate the rôle of histamine in the external mechanism of the skin reaction to tuberculin, reports definite blocking or decreasing in intensity of tuberculin reactions in humans following the use of an antihistamine agent (Antergen), although no statement is made regarding the amount of tuberculin employed or details of the test procedure.

Because it is standard procedure to use threshold doses in most bioassay work, we decided to investigate the effect of Benadryl hydrochloride on threshold doses of tuberculin, i.e., doses causing only low-degree skin reactions. Larger amounts of tuberculin were included to explore the possibility of a relationship between dosage and reaction.

## EXPERIMENTAL

The study was divided into two parts. Considered first was the investigation of the possible effect of an antihistamine agent on the tuberculin reaction produced by tuberculin, Purified Protein Derivative (P.P.D.) prepared by the ammonium sulfate precipitation method of Seibert. Secondly, the study was repeated employing Tuberculin Old, Koch, as the tuberculin testing material.

<sup>1</sup>  $\beta$ -dimethylaminoethyl benzhydryl ether hydrochloride (diphenhydramine hydrochloride), Parke, Davis & Company.

<sup>2</sup> From the Research Laboratories, Parke, Davis & Company, Detroit 32, Michigan.

As previously stated, we wished to employ threshold doses of tuberculin. Because tuberculin, Purified Protein Derivative first strength (0.00002 mg.) sometimes fails to elicit a positive tuberculin reaction in weak reactors (10), and the same is true with 1:10,000 Old Tuberculin, these doses were considered suitable for threshold levels and included along with two higher levels of each tuberculin used.

### *Sensitization of Guinea Pigs to Tuberculin*

Healthy white guinea pigs of 350–400 grams weight were given intraperitoneally a suspension of mixed human and bovine strains of *M. tuberculosis* following a predetermined dosage plan that has been employed repeatedly to induce tuberculin sensitivity in this laboratory. Animals were weighed at the time of inoculation and at weekly intervals until used. The infected guinea pigs gain weight for about three weeks after inoculation and the weight then tends to level off. Death will ordinarily occur ten to fourteen weeks after inoculation.

#### *I. Effect of Benadryl on the Purified Protein Derivative Tuberculin Reaction*

*Tuberculin Testing of Guinea Pigs Prior to Benadryl Administration.* The interpretation of the effect of Benadryl on the tuberculin reaction was controlled by the tuberculin testing of sensitized guinea pigs before and after Benadryl administration. Four to six weeks after infection with *M. tuberculosis*, the hair was removed from the left half of the backs of 25 guinea pigs and each animal received 0.00002 mg., 0.0005 mg., and 0.005 mg., of Tuberculin Purified Protein Derivative intradermally. The skin reactions were read on the basis of extent of reactions in millimeters after 24 and 48 hours.

*Benadryl Administration.* Forty-eight hours after the second tuberculin reading, 22 of the guinea pigs were given Benadryl subcutaneously as a 1 per cent aqueous solution at the rate of 50 mg. Benadryl per kilo body weight per day in 2 divided doses at the beginning and close of the laboratory day. Benadryl administration was continued for four days and carried through the second tuberculin testing period. Three guinea pigs received no Benadryl and served as a control on the intensity of the tuberculin reaction itself. Weight checks showed no weight losses among the test animals during the period of Benadryl administration. While we realized the possibility of risking toxic manifestations with this quantity of Benadryl, it was considered wise to be sure we were not failing to block reactions because of insufficient Benadryl concentration. Also, the effect of this high dosage was considerably modified by slower absorption when administered subcutaneously, and the dividing of the daily amount into 2 doses.

*Tuberculin Testing after Benadryl Administration.* Forty-eight hours after the initial Benadryl dose, the 22 test guinea pigs and the 3 control guinea pigs were retested with Tuberculin P.P.D. on the right half of the backs, employing the same amounts of tuberculin as before. Benadryl administration was continued throughout the tuberculin test period and skin reactions again read at 24 and 48 hour intervals.

Results of tuberculin testing with Tuberculin P.P.D. before and after Benadryl are shown in table I.

TABLE I  
*Effect of Benadryl on the tuberculin P.P.D. reaction in 22 guinea pigs*

AMT. OF TUBERCU- LIN P.P.D.	TEST TIME	TIME OF READING	NO. OF REACTIONS ACCORDING TO AREA IN SQUA: MILLIMETERS					
			0-75	76-150	151-225	226-300	301-375	376 and over
mg. 0.00002	Before Benadryl After Benadryl	24	2	11	9	0	0	0
			22	0	0	0	0	0
	Before Benadryl After Benadryl	48	19	3	0	0	0	0
			22	0	0	0	0	0
0.0005	Before Benadryl After Benadryl	24	0	1	10	9	1	1
			11	9	2	0	0	0
	Before Benadryl After Benadryl	48	9	13	0	0	0	0
			22	0	0	0	0	0
0.005	Before Benadryl After Benadryl	24	0	0	1	0	7	14
			1	8	10	1	1	1
	Before Benadryl After Benadryl	48	0	12	7	3	0	0
			18	1	3	0	0	0
0.00002	Before Benadryl No Benadryl (cont)	24	0	3	0	0	0	0
			1	2	0	0	0	0
	Before Benadryl No Benadryl (cont)	48	3	0	0	0	0	0
			3	0	0	0	0	0
0.0005	Before Benadryl No Benadryl (cont)	24	0	1	2	0	0	0
			0	1	2	0	0	0
	Before Benadryl No Benadryl (cont)	48	2	1	0	0	0	0
			2	1	0	0	0	0
0.005	Before Benadryl No Benadryl (cont)	24	0	0	0	0	0	3
			0	0	0	0	0	3
	Before Benadryl No Benadryl (cont)	48	0	0	3	0	0	0
			0	0	3	0	0	0

## II. Effect of Benadryl on the Old Tuberculin Reaction

Because the results obtained with Benadryl and tuberculin P.P.D. were not in agreement with those previously reported by others (8) using Old Tuberculin, it was thought expedient to check the possibility that the difference in results

was due to the wide chemical difference in the types of tuberculin employed. The Tuberculin, P.P.D. which was employed is relatively free (less than 5 per cent) of components other than tuberculo-protein, while Tuberculin Old is a crude material containing all culture medium constituents and bacterial degradation and metabolic products, and the possibility was considered that it was the reactions to these substances or the lower molecular weight tuberculo-protein fractions which were not being blocked by antihistamine agents.

The procedure followed for testing the effect of Benadryl on the tuberculin, P.P.D. reaction was repeated. Thirty-five tuberculous guinea pigs received Tuberculin Old, Koch, intradermally at 1:100, 1:1000, and 1:10,000 levels. Reactions were read at 24 and 48 hours. Seventy-two hours later a course of Benadryl was initiated in 30 guinea pigs according to the previous time and dosage schedule. Five animals were retained as a control on the intensity and regularity of the tuberculin reaction. Forty-eight hours after the initiation of Benadryl administration, the 35 guinea pigs were again tuberculin tested with Old Tuberculin, Koch, on the same levels as used in the initial tests. Reactions were read 24 and 48 hours later with Benadryl continued throughout the test period. Results are shown in table II.

#### RESULTS

The data obtained from the experimental work can be treated in two ways based upon 1) the presence or absence of a tuberculin skin reaction and 2) a graded response of the skin to tuberculin. Tables I and II give the overall summary of the reactions produced before and after Benadryl with tuberculin, P.P.D. and Tuberculin Old, Koch, respectively. Examination of these tables indicates that there appears to be a definite trend in the direction of lessening of tuberculin reactions after Benadryl administration.

Table III summarizes the results according to the presence or absence of skin manifestations in guinea pigs receiving the small or threshold doses of tuberculin, and clearly indicates that Benadryl protected the skin from developing a tuberculin reaction in 50 per cent of the guinea pigs from 0.00002 mg. of tuberculin P.P.D. in 24 hours, and in 23.3 per cent of the guinea pigs from 1:10,000 Tuberculin Old, Koch, in 24 hrs. When a large dose of Tuberculin Old, Koch, was given (1:10 dilution), considerable necrosis was encountered. The use of Benadryl brought about a lessening of the necrotic effect in all guinea pigs on retesting and in 78 per cent of the animals necrosis was suppressed up to the end of a 48 hour observation period. Statistical analysis<sup>3</sup> of these results are also shown in table III and the  $X^2$  test shows these results to be statistically significant.

To elucidate the quantitative effect of Benadryl on the tuberculin reactions shown in tables I and II, the latter were graded by the skin area which responded. The mean of a number of determinations in individual animals and the standard error of the mean were calculated according to the conventional

<sup>3</sup> Grateful acknowledgment to Dr. Graham Chen for assistance in statistical analysis of our data.

methods (S.E.,  $\frac{\sigma}{N}$ ;  $\sigma$  standard deviation; N, number of determinations). If desired the mean values of response  $\pm 3$  S.E. to the different doses of tuberculin may also be plotted graphically to reveal two points of statistical significance:

TABLE II  
*Effect of Benadryl on the tuberculin Old, Koch reaction in 50 guinea pigs*

AMT. OF TUBERCULIN OLD, KOCH	TEST TIME	TIME OF READING	NO. OF REACTIONS ACCORDING TO AREA IN SQUARE MILLIMETERS					
			0-75	76-150	151- 225	226- 300	301- 375	376 and over
0.1 cc. 1:1000 dilution (1:10,000)	Before Benadryl After Benadryl	24 <i>hrs.</i>	4	14	9	3	0	0
			27	3	0	0	0	0
	Before Benadryl After Benadryl	48	24	5	1	0	0	0
			30	0	0	0	0	0
0.1 cc. 1:100 di- lution (1:1000)	Before Benadryl After Benadryl	24	0	3	8	8	6	5
			2	15	9	3	0	1
	Before Benadryl After Benadryl	48	3	16	9	0	1	1
			14	16	0	0	0	0
0.1 cc. 1:10 di- lution (1:100)	Before Benadryl After Benadryl	24	0	0	0	1	1	28
			0	0	3	5	7	15
	Before Benadryl After Benadryl	48	0	2	3	1	6	18
			2	7	12	6	2	1
0.1 cc. 1:1000 dilution (1:10,000)	Before Benadryl No Benadryl (cont)	24	1	3	1	0	0	0
			1	2	2	0	0	0
	Before Benadryl No Benadryl (cont)	48	4	1	0	0	0	0
			4	1	0	0	0	0
0.1 cc. 1:100 di- lution (1:1000)	Before Benadryl No Benadryl (cont)	24	0	0	1	0	1	3
			0	0	1	1	0	3
	Before Benadryl No Benadryl (cont)	48	0	4	0	1	0	0
			0	3	1	1	0	0
0.1 cc. 1:10 di- dilution (1:100)	Before Benadryl No Benadryl (cont)	24	0	0	0	0	0	5
			0	0	0	1	0	4
	Before Benadryl No Benadryl (cont)	48	0	0	0	0	1	4
			0	0	0	2	1	2

1) a quantitative relationship between inoculating dose and the skin reaction and 2) a difference in response before and after Benadryl. By the same means the linear relationship between dose and response may possibly be utilized to

determine the potency of a tuberculin of unknown strength while the slope of the line may reveal the nature of the tuberculin preparation. This work is being continued. The effect of Benadryl is indicated by the corresponding lower parallel lines; its presence does not seem to change the slope of the dose-response curve.

The two means of skin reactions with the same inoculating dose of tuberculin before and after Benadryl were also compared by the test of significance of difference. The "t"<sup>4</sup> values are 6.2 to 12.4 for tuberculin, Purified Protein Derivative and 5.3 to 8.5 for Tuberculin Old, Koch, for 44 and 60 determina-

TABLE III

*Effect of Benadryl on tuberculin reaction in guinea pigs*

NUMBER OF ANIMALS USED	DOSAGE OF TUBERCULIN	NUMBER OF ANIMALS GIVING POSITIVE TUBERCULIN REACTION*				% PROTECTION BY BENADRYL		oX <sup>†</sup>	
		Before Benadryl		After Benadryl					
		24 hr.	48 hr.	24 hr.	48 hr.	24 hr.	48 hr.	24 hr.	48 hr.
22	0.00002 mgm. P.P.D.	22	22	11	1	50.0	95.5	14.6	40.2
30	0.1 cc. 1:10,000 O.T. Koch	30	29	23	6	23.3	80.0	7.9	36.2
30	0.1 cc. 1:100 O.T. Koch		28‡		6‡		78.6		32.1

\* In control experiments it was shown that the skin sensitivity to tuberculin was not diminished by the previous injection of the material.

$$oX^2 = \frac{(ad - bc)^2 (a + b + c + d)}{(a + b)(c + d)(a + c)(b + d)}$$

Page 19, Statistical Method by Sencdecor.

† P = 0.01 for X<sup>2</sup> 6.635; P < 0.01 for these values.

‡ Number of skin reactions with necrosis.

tions respectively with various doses of tuberculin. The "P" value is therefore practically nil. In other words, the difference of means (before and after Benadryl) is statistically significant. In control animals in tables I and II, the skin sensitivity of the guinea pigs was tested for an acquired resistance to tuberculin following injection of this material. There was no difference in skin reactions in successive inoculations (t = 0.00 to 1.28 for 10 determinations each of 1:10,000 to 1:100 Tuberculin Old, Koch).

It is possible that these results can be credited to one or both of 2 factors: 1) the use of the threshold values of tuberculin discussed previously and 2)

$$t = \frac{M_1 - M_2}{\sqrt{\frac{N_1 N_2}{N_1 + N_2} + \frac{N_1 \sigma_1^2 + N_2 \sigma_2^2}{N_1 + N_2 - 2}}}$$

M = Mean; N = Number of determinations.  
σ = Standard deviation.

the repeated use of large amounts of antihistamine compound to effect a maintenance of a constant high level in the tissues. Benadryl has been shown by Chen (11) to maintain a high concentration in the tissues for approximately 6 hours after subcutaneous administration. On the basis of this, since the guinea pig tuberculin reaction usually reaches its highest intensity in about 24 hours, our guinea pigs were maintaining a high level of antihistamine agent throughout the test period.

#### CONCLUSIONS

In adequate dosage levels, Benadryl gave a reduction in the tuberculin skin reaction and markedly reduced the incidence of necrosis.

When threshold amounts of tuberculin were used, Benadryl made many reactions fail entirely to develop in twenty-four hours and most reactions fail to appear after forty-eight hours.

Because most tuberculin testing of both adults and children is started at the so-called threshold levels of tuberculin (0.000,02 mg. of tuberculin, Purified Protein Derivative or 1:10,000 Old Tuberculin), in order to reduce the possibility of severe reactions, it is important to determine whether the individual being tested is receiving any antihistamine compound at the time of tuberculin testing before correct interpretation of a negative reading can safely be made.

#### CONCLUSIONES

*Efecto del Clorhidrato de Benadrilo sobre la Reacción a la Tuberculina en el Cobayo*

A dosis adecuadas, el Benadrilo logró una reducción en la cutirreacción a la tuberculina y rebajó considerablemente la incidencia de esfacelo.

Cuando se emplearon dosis límites de tuberculina, el Benadrilo hizo que muchas reacciones no aparecieran en absoluto en 24 horas y que la mayor parte no se presentaran al cabo de 48 horas.

Como la mayor parte de la comprobación con tuberculina tanto en adultos como niños se inicia con la llamadas dosis umbrales o límites de tuberculina (0.000,02 mg. el Derivado Proteínico Purificado de Tuberculina o Tuberculina Antigua al 1:10,000) a fin de mermar la posibilidad de reacciones graves, resulta importante determinar si el individuo comprobado recibe algún compuesto antihistamínico al hacerse la prueba para poder así interpretar correctamente una lectura negativa.

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## MEDICAL ASPECTS OF REHABILITATION<sup>1, 2</sup>

### A Study on 175 Veterans with Arrested Pulmonary Tuberculosis

IRVING PINE<sup>3</sup>

Since the Veterans Administration is embarking on a vast program of rehabilitation for the tuberculous veteran which in its size and scope will probably exceed any other similar program in the United States (1), it was thought that the study of a large group of arrested cases would yield valuable information in making such a program more effective.

In order to obtain a many-sided view of the arrested case regardless of the type of treatment employed, a study was undertaken of all patients with arrested pulmonary tuberculosis at the largest veterans' tuberculosis hospital located at Oteen, North Carolina, from March 1, 1946 to February 28, 1947.

For the twelve-month period studied, the tuberculosis admissions were 917 and the average daily census for the hospital during that period was 963. The number of discharges for tuberculosis was 1,143 in the period stated which included 177 patients dying of pulmonary tuberculosis and 175 discharged as arrested pulmonary tuberculosis.

This study concerns itself with the arrested patients among whom are included men and women veterans, both Negro and white, who fulfilled the criteria of arrest according to the National Tuberculosis Association classification.

"The arrested case . . . constitutional symptoms are absent, sputum if any, must be concentrated and found microscopically negative for tubercle bacilli, lesions stationary and apparently healed according to X-ray examination with no evidence of pulmonary cavity. These conditions shall have existed for a period of six months, during the last two of which the patient has been taking one hour's walking exercise twice daily or its equivalent" (2).

#### SEX, AGE, AND COLOR

At the time of discharge 151 male patients and 24 female patients were classified as arrested cases. The patients are classified by sex and color in table 1.

Of the males 123 were veterans of World War II with a median age of 26 years, while the median age of the 21 female veterans of World War II was 25. The youngest World War II veteran was 19 years of age at the time of his discharge from the hospital and the oldest was 53. Male veterans of World War II who were discharged with arrested disease in the minimal stage were on the

<sup>1</sup> From the Veterans Administration Hospital, Oteen, North Carolina.

<sup>2</sup> Published with permission of the Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

<sup>3</sup> Formerly Physician-in-Charge, Medical Rehabilitation, Veterans Administration Hospital, Oteen, North Carolina. Resigned May 1, 1947. Present address: 58 St. Dunstan's Road, Asheville, North Carolina.



average older than those whose disease had progressed to a more advanced stage (see table 2).

The importance of these age figures is that the male World War II veterans especially are the essential wage earners who must assume responsibilities in the

TABLE 1

*Tuberculous veterans of World War I and World War II who were discharged as arrested from Oteen Veterans' Hospital March 1, 1946-February 28, 1947, classified by sex and color*

SEX AND COLOR	TUBERCULOUS VETERANS		
	Both wars	World War I	World War II
Both sexes.....	175	31	144
White.....	155	29	126
Negro.....	19	1	18
Chinese.....	1	1	—
Male.....	151	28	123
White.....	133	26	107
Negro.....	17	1	16
Chinese.....	1	1	—
Female.....	24	3	21
White.....	22	3	19
Negro.....	2	—	2

TABLE 2

*Male tuberculous veterans of World War II and median age at time of discharge as arrested from Oteen Veterans' Hospital March 1, 1946-February 28, 1947, classified by stage of disease upon discharge*

STAGE OF DISEASE UPON DISCHARGE	MALE TUBERCULOUS VETERANS OF WORLD WAR II	
	Number discharged	Median age at discharge
All stages.....	123	26
Minimal.....	24	29
Moderately advanced.....	58	27
Far advanced.....	41	26

community after spending the best years of their lives in military service and afterwards fighting tuberculosis. The rehabilitation of these men is therefore of paramount importance.

The median age of the veterans of World War I was 51 years. The youngest was 45 and the oldest World War I veteran was sixty-three years of age at the time of discharge from the hospital. Among the World War I veterans, because of their more advanced age, it is a matter of great speculation as to how

much rehabilitation can accomplish, especially since practically all of them are in the moderately advanced and far advanced groups.

The 24 female patients who were discharged as arrested cases present problems related not only to rehabilitation in general, but also in relation to marital life, housekeeping, and in 12 of them, the question of return to the nursing profession. It would seem to be a simple solution to allow nurses to work part-time for graded periods depending upon their condition, in the hospital of their "cure" or in any other appropriate hospital. Nevertheless, despite the nursing shortage and the various plans for rehabilitation, the practical needs of these nurses go unsolved because it is almost an impossibility for them to find such positions.

#### LENGTH OF HOSPITALIZATION

The average total hospitalization period for all patients was about 26 months, while the time spent at Oteen was about 21 months. In this connection the average period of five months spent at another hospital was usually either in an army or navy hospital before transfer to the Veterans' Administration. With

TABLE 3

*Tuberculous veterans of both wars who were discharged as arrested from Oteen Veterans' Hospital March 1, 1946-February 28, 1947; average number of months spent in all hospitals and at Oteen, classified by sex*

SEX	TUBERCULOUS VETERANS DISCHARGED	AVERAGE NUMBER OF MONTHS SPENT	
		In all hospitals	At Oteen
Both.....	175	25.8	20.9
Male.....	151	25.1	20.3
Female.....	24	29.7	25.0

the cessation of hostilities, therefore, there will probably be a slightly longer period of hospitalization at the Veterans' Hospital and perhaps a slightly shorter period of total hospitalization for future arrested cases (see table 3).

It is striking that the minimal cases and the moderately advanced cases with negative findings require practically the same length of hospitalization. The far advanced cases required at least 12 months longer than the minimal cases, and from six to eight months longer than the moderately advanced positive cases. The shortest period of hospitalization was ten months (see table 4).

#### TREATMENT

It is not within the scope of this paper to evaluate the treatment in the various types of disease for each individual patient. However, in order to appreciate the problem of after-sanatorium care and rehabilitation procedures not completed while hospitalized, an estimate of the type of treatment is important.

In this group of cases, 54 patients were treated symptomatically and with rest. For the most part, these non-collapse cases were in the minimal and moderately advanced groups.

TABLE 4

*Tuberculous veterans of both wars who were discharged as arrested from Oteen Veterans' Hospital March 1, 1946-February 28, 1947; average number of months spent in all hospitals and at Oteen, classified by stage of disease and sputum status*

ADMISSION STAGE OF DISEASE AND SPUTUM STATUS	TUBERCULOUS VETERANS DISCHARGED	AVERAGE NUMBER OF MONTHS SPENT	
		In all hospitals	At Oteen
All stages.....	175	25.8	20.9
Minimal.....	32	20.9	15.6
Positive sputum.....	15	20.6	14.8
Negative sputum.....	17	21.3	16.3
Moderately advanced.....	83	22.7	18.8
Positive sputum.....	61	24.5	20.0
Negative sputum.....	22	18.0	15.8
Far advanced.....	60	32.5	26.6
Positive sputum.....	59	32.5	26.6
Negative sputum.....	1	25.0	19.0

TABLE 5

*Tuberculous veterans of both wars with specified stage of disease and sputum who were discharged from Oteen Veterans' Hospital March 1, 1946-February 28, 1947, classified by type of therapy*

TYPE OF TREATMENT	VETERANS WITH SPECIFIED STAGE OF DISEASE AND SPUTUM STATUS						
	Total	Minimal		Moderately advanced		Far advanced	
		Posi- tive	Nega- tive	Posi- tive	Nega- tive	Posi- tive	Nega- tive
All.....	175	15	17	61	22	59	1
Symptomatic treatment and rest.....	54	7	12	17	13	4	1
Pneumoperitoneum and phrenic crush...	14	—	—	2	—	12	—
Thoracoplasty and revision.....	13	—	—	1	—	12*	—
Pneumothorax.....	25	1	—	15	—	9†	—
Phrenic crush and rest.....	21	7	5	—	9	—	—
Other types of treatment difficult to evaluate.....	48‡	—	—	26	—	22	—

\* Includes one lobectomy.

† Includes one bilateral pneumothorax.

‡ Includes veterans treated by phrenic crush, those whose pneumothoraces were abandoned, and those treated by rest.

The total number of patient phrenics was 93, while 83 pneumothorax attempts were made. Pneumonolyses numbered 18.

Fourteen patients were discharged with pneumoperitoneum following a phrenic crush on the side of cavity or more extensive disease. Thoracoplasty operation was used in 13 cases including one lobectomy case. Pneumothorax was effective

in 25 patients, 18 of whom required pneumonolysis. Whereas the pneumoperitoneum and thoracoplasty cases had far advanced disease, more than one-half of the pneumothorax cases were for moderately advanced disease (see table 5).

In evaluating the disability of these patients, one must have in mind that almost all of the cases of collapse therapy have limited respiratory function which would certainly preclude gainful employment where undue amounts of exertion are required. Although the phrenic crush was done in 90 patients, this was invariably a supplementary procedure to other forms of collapse therapy or in conjunction with bed rest. It is well to remember that phrenic operations alone can induce limited respiratory function which becomes more apparent on exertion (3).

In all cases of pulmonary tuberculosis regardless of the type of therapy employed, an awareness of the latent and manifest complications such as bronchiectasis, emphysema, chronic bronchitis, and pulmonary fibrosis is important in evaluating the extent of graded activity of the person with arrested disease.

In this series there was no correlation between the type of treatment used and the total period of hospitalization.

#### SPUTUM CONVERSION

As a general rule, the examinations for tubercle bacilli following treatment were at least as intensive and as numerous as before treatment. It was startling in this study that 59 patients had one positive sputum (or gastric lavage) by concentration or culture some time after apparently successful treatment and sputum conversion. If one adhered to very rigid criteria, as happened in some of these patients, hospitalization was not only prolonged but certain disturbing mental phenomena appeared, which in the light of the continuing favorable course of these patients was not justified. From the practical point of view, one must recognize that one swallow doesn't make a summer; nor in the treated case does one positive sputum or an occasional positive culture mean a "breakdown" (4).

In 15 patients during the period of graded activity the sputum (or gastric lavage) returned positive. This development prolonged the period of hospitalization for four to six months in seven of these cases, whereas the other eight proceeded as though the finding of a positive culture on one occasion could occur with clinical, laboratory, and X-ray findings essentially unchanged.

Since the mark of a successfully treated case is a bacillus-free patient, the appearance of one positive sputum or an occasional positive culture should be properly evaluated. And it should not be assumed that it means a spread or progression of the disease.

#### GRADED ACTIVITY

The procedure followed in most of these cases was to increase the exercise gradually for the last six months so that in the last four months they were known as ambulatory patients who would be graded up to two to four hours' walking exercise daily. Thirty-five patients followed educational studies or vocational pursuits in newly set up "shops" for this purpose.

Up to a few months ago the patient's temperature, pulse, and respiration were

recorded before and after hiking and then one-half hour later. This record constituted the exercise chart. But by practical application it was found that the patient's condition was considered altered only by a change in sputum or in the X-ray or in a few instances because of bronchoscopic examination.

Hence, the value of the daily hiking check-up becomes obsolete not only in practice but in theory. Now the procedure is to advise and encourage each patient to take more purposeful activity within graded periods of time as outlined in consultation between the ward physician and the Department of Medical Rehabilitation.

It has been previously mentioned that seven patients had more than a four months' ambulatory period because of positive sputum findings. And yet, only

TABLE 6

*Male and female tuberculous veterans of both wars who were discharged as arrested from Oteen Veterans' Hospital March 1, 1946-February 28, 1947, classified by socio-economic status*

SOCIO-ECONOMIC STATUS	VETERANS OF BOTH SEXES	MALE VETERANS	FEMALE VETERANS
All groups* . . . . .	175	151	24
Professional and managerial workers . . . . .	26	14	12†
Clerical, sales, and kindred workers . . . . .	27	19	8
Skilled workers . . . . .	17	16	1
Semi-skilled workers . . . . .	18	18	—
Unskilled workers . . . . .	26	26	—
Service workers‡ . . . . .	18	17	1
Agricultural workers and fishermen . . . . .	21	21	—

\* Not classifiable by occupation were 22 students: 20 males and 2 females.

† These 12 female veterans were nurses.

‡ Includes domestic, personal, and protective service workers.

two of these had questionable X-ray changes and two were held up because of bronchoscopic findings.

The progress of the patient with pulmonary tuberculosis through graded activity, sheltered work, and perhaps full tolerance would therefore seem to be related more to the state of the pulmonic lesion than to the results of work tolerance tests.

#### SOCIO-ECONOMIC STATUS

The patients were classified according to the Dictionary of Occupational Titles issued by the United States Employment Service (5). The only study of death rates by occupation (6) ever made in this country indicates that the greatest mortality from tuberculosis occurs among unskilled workmen of all ages. The next highest mortality is usually found among semi-skilled workers.

The socio-economic status of the discharged veterans included in this study, based on their former occupations, is shown in table 6.

These are important figures in planning any rehabilitation program. Among

the male veterans, students and unskilled workers should be directed along lines which will lead them to choose favorable occupations. In the skilled group of workers who have financial security, the rehabilitation advisor should concern himself more with hours per day of work rather than with change of occupation. In the clerical, service, and agricultural fields, unless a change of occupation is indicated or desirable, rehabilitation should concern itself especially with the number of hours of work.

Vocational guidance must not only be a means of choosing an occupation, but must also consist of medical advice as to the hours of work per day indicated. Except for 14 male patients in the professional group, all required vocational guidance and medical advice concerning their future occupation.

### SECOND "CURES"

Thirteen patients in this group have been cured for the second time and one of these for the fourth time. Each one had previously been given an arrested diagnosis. Seven of these were negative cases on the second admission and the remaining six were positive. All these patients were difficult problems, because in addition to the fact that they emphasize dramatically the danger of recurrence, they had to be given special confidence and attention to fortify them against introspection which characterizes their thinking about future breakdowns.

For example, four of these were nurses who were extremely disillusioned about ever returning to their profession. They stated that it was not only impossible for them to obtain light work, but that they worried continually about recurrence. It requires patience, tact, and an explanation relating the value of productive work in the life of contented human beings, more so in the group of patients taking the second "cure."

### DISCUSSION

The course of the disease is different in every patient with arrested pulmonary tuberculosis. It has been shown in this series that so much time is spent in hospitalization that rehabilitation procedures must therefore loom large in the daily life of the patient.

For the bed patient relaxation therapy (7) and bed exercises when indicated must be considered. For the thoracoplasty patient corrective physical exercises and posture must be taught and practiced pre- and postoperatively. For all patients beginning graded activity, a rehabilitation evaluation including vocational guidance should begin as soon as practicable and be directed along the lines of greatest satisfaction for the patient. It is in this manner that rehabilitation procedures can keep pace with the rest of the treatment in each individual case.

### SUMMARY

1. Medical aspects of rehabilitation in 175 veterans with arrested pulmonary tuberculosis are discussed.

2. The average length of hospitalization was about two years. The median age of World War II veterans at the time of discharge was 26 years. No correla-

tion was noted between the type of treatment used and the total period of hospitalization.

3. In 59 patients during treatment and after sputum conversion, the sputum became positive again. While in 15 of these patients this development occurred during the last six months, in the period of graded "activity," one positive sputum does not constitute a "breakdown."

4. The important factor in the health of the patient is the state of his pulmonary lesion. The important factors in rehabilitation are the future occupation of the patient, the hours of work to be done, and the knowledge that rehabilitation must proceed as part of the treatment.

5. Proper occupational guidance for all patients will prevent disturbing mental reactions to their illness.

#### SUMARIO

##### *Aspectos Médicos de la Rehabilitación*

1. Discútense las fases médicas de la rehabilitación en 175 veteranos con tuberculosis pulmonar estacionada.

2. La hospitalización promedió unos dos años. La edad media de los veteranos de la II Guerra Mundial, al darlos de alta, fué 26 años. No se notó correlación alguna entre la forma de tratamiento utilizada y el período total de hospitalización.

3. En 59 enfermos durante el tratamiento y después de haber virado el esputo, éste se volvió positivo de nuevo. Aunque en 15 de los enfermos esto sucedió durante los últimos seis meses, en el período de "actividad" graduada, un esputo positivo no constituye una "desintegración."

4. El factor importante en la salud del enfermo es el estado de la lesión pulmonar. En la rehabilitación los factores importantes son: la futura ocupación del sujeto, las horas que debe trabajar y el conocimiento de que la rehabilitación debe proseguir como parte del tratamiento.

5. La debida orientación profesional de todos los enfermos impedirá la aparición de reacciones mentales perturbadoras a su enfermedad.

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# THE RÔLE OF THE FAMILY IN THE CONTROL OF TUBERCULOSIS<sup>1</sup>

HOLLAND HUDSON<sup>2</sup>

Health workers, on noting the title of this session, will assent to its implication in some general term as: "Yes, the family is very important." However, in practice, many of our efforts at tuberculosis control attempt to deal with the sick individual as if he were an independent entity. We are prone to regard the tuberculous patient as a focus of infection, dangerous to his fellows, and to forget the controlling factors that the patient is a person and that patients have families. We need to be reminded frequently that the most skilled medical treatment can produce limited result without the cooperation of the tuberculous patient and his family in the community effort to control and conquer tuberculosis.

Unless we have given the subject some careful scrutiny, our concept of the family tends to be limited and colored by personal experience. To some persons, the family is "me and my wife, my son John and his wife, us four and no more." To certain academic sociologists, the family consists of two parents and three children and the greater part of their theories and conclusions are built around such groupings, excluding all others. We happier persons who are no sociologists need not become highly technical in order to consider the ways in which the family, in its various forms and manifestations, affects the individual's response to diagnosis, treatment, and recovery from tuberculosis. We can apply a little orderly enumeration of the influences represented without poaching on the preserves of this science.

Each of us began life as a child and each of us is influenced very considerably throughout our lives by the parents who bore us and reared us and by the brothers and sisters with whom we grew up. These influences tend to be indelible. Their effect may be modified more or less by other influences and experiences, but unless a great deal of such modification takes place, our home influences are likely to live with us while we live. Long after an individual is laid to rest, certain of his physical characteristics persist, not only in his immediate offspring, but in succeeding generations. This kind of immortality is not limited to the physical realm. It extends considerably into the group traditions and customs.

To illustrate: Here, on the one hand is a family in which the privacy of the individual is respected and protected. He may be alone when he chooses, for thought, for prayer, for work, or for change of garments. Throughout life such a man or woman will expect and demand privacy for himself and for others, privacy from the eyes and ears, from the chatter and the noise of others. Such

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sudden mobilizations as war disclose other families, not far away from those I have just mentioned, in which personal privacy has no place whatsoever. In these other families, the individual is continuously exposed to the eyes and ears and tongues of other members of the family and sometimes to those of the public as well. In this group, individual thought and action may receive a minimum of encouragement.

To make a brief application of this illustration to our subject of tuberculosis control: may we expect similar responses to diagnosis, case finding, contact checking, and treatment situations from two individuals so differently reared? Both may resist our efforts at disease control, but probably for diametrically different reasons. To one individual, the course we recommend is a surrender of cherished privacy. Under the most favorable treatment conditions this patient is examined and reexamined by doctors, interns, and sometimes, by medical students. Meals are served at the convenience of the staff, not the patient. Members of the technical staff take histories, collect blood and sputum samples. Even a "private" room is invaded by nurses, maids, orderlies, and porters at their own convenience. Even a small ward is, to this individual, an indecent exposure.

To another, separation from the accustomed family goldfish bowl may provide the obstacle. All of his carefully nurtured extroversion is no defense against the alien characteristics of his new surroundings. All of these persons about him now are strangers and they are not particularly interested in what he has to say. He may not circulate; he must remain in his bed. Never before has he felt so helpless, so insignificant and frustrated. It is unlikely that we shall understand and neutralize the resistance of either patient until we study the group which continues to influence him.

After that introductory sampling of two kinds of influence of families upon individuals which are presented in order to emphasize why it is important to understand the individual in terms of his past experience, we may attempt, for purposes of convenience, a rough classification of types of significant influences upon individual behavior. We all know that such categorical separations are over-simplification, valuable chiefly as aids to exposition and to memory. The separation between genetic influences and environmental influences is arbitrary and artificial, in our present state of knowledge. It is difficult to say where one leaves off and the other begins.

First, then, come the genetic influences, both physical characteristics and those related traits, which we inherit. Sometimes, in violent reaction against the absurd recurrence of "he takes after" in old wives' tales, we discount too far the degree to which our lives and our behavior are affected by inheritance.

The second category of influence upon the behavior of the individual is that of environment. The homes in which we are reared are the sources of lifelong threads of influence of which we are not always personally aware. This category may include both cultural and habit factors. It is easy for an observer to identify the manner, the idiom, the accretion of habits which take place as a result of the close association of a family group. The attitudes of the family often determine many of the future attitudes of its individual members. In

the pattern of everyday family living is determined for many years whether the individual's impulses and behavior tend to be social, asocial, or anti-social. Out of one environment may come a suspicious, truculent and provincial individualist; out of another, a considerate, cooperative, and urbane type of citizen. Bystanders, including health workers, educators and others may be quite unconscious of such trends until the child, who has now become an adult, comes into possession of something inimical to the safety of others, such as a flourishing colony of tubercle bacilli.

Environmental influence has a wider rim than the family circle itself. The characteristics of the family may be affected by its geographic origin, its settlement in rural or city surroundings, or by migration from one to the other. One might cite the example of families who have migrated from rural Kentucky into the cities of Southern Indiana and Western Ohio. These people are often highly sensitive regarding the opinion of their cultures held by their new neighbors. The location of a home on the preferred or on the despised side of the railroad tracks may leave its imprint on the assurance or the insecurity of the family and its members. Adequate or inadequate housing may affect both family and individual attitudes as well as the opportunities for infection.

A third factor in individual attitudes and behavior is the emotional nature of the individual himself. This is sufficiently autonomous in many respects to raise a fair question whether it belongs in a listing of the types of family influence. But it is in continuous reaction to the two other factors, to people and to situations. Let us consider, for example, an individual whose genetic endowment includes a tendency to nutritional deficiency and whose emotional nature is driving and ambitious. To this individual, whose body will not carry through what he would like to accomplish, patience does not come easily. His endowment tends to make him critical of his environment. This triad of factors makes an individual who is seldom easy to live with, and who is unlikely to give a docile response to advice should he contract active pulmonary tuberculosis.

The emotional interaction between the members of any family supplies many of the harmonies and dissonances by which the rest of the family are affected and influenced. The dominant parent may provoke fear or respect or rage in his offspring. Often the individual response of each member of the family differs from that of the others.

But those influences of our formative years are not the end of the tendency of the family to affect the behavior of the adult. When an adult marries, a modification of personality begins which continues as long as the parties continue living together. If there is insufficient modification, as sometimes happens, the marriage is, at best, less than completely successful and the tensions created may lead to a complete break. As we study the behavior of couples, we may note that the married man or woman brings to his future existence, not only the three categories of influence which have affected his own childhood and adolescence, but that he now takes on, sometimes very directly, the influences which affect his marital partner. To consider a married couple without issue as something less than a family is to ignore a major source of adult behavior.

No statistical literature is available on a numerical correlation between tuber-

culosis and broken homes. Even if such statistics were available we should regard them skeptically, unless it was entirely clear that the compiler never lost sight of the fact that the etiology of tuberculosis is the tubercle bacillus. However, clinical experience yields some pertinent case histories concerning this correlation. In more than a few instances, the onset of clinical disease has been preceded by an interval of acute emotional tension which may have helped to lower the threshold of immunological resistance. Young married couples sometimes find great difficulty in adjusting to their mutual problems or to the behavior of their in-laws. Breadwinners and homemakers, seeking to cope with growing responsibilities and shrinking purchasing power, may experience intense anxieties, in the psychiatrist's application of the term.

Tuberculosis occasionally provides the detonator for disagreements between couples whose previous relationship has been precarious or may supply a major irritant in such disagreement. Fear of the disease by one of the parties or by his family frequently motivates or helps to rationalize neglect and desertion. A separation enforced by hospitalization may so inflame jealousies and mistrust in one partner or the other, with or without cause, as to end any amicable relationship.

In this connection, one frequent symptom of tuberculosis not often included in our usual listings, is a growing emotional irritability. Many a patient has made, in the depths of his fatigue before diagnosis, emotional over-statements which have affected much of his future, whether by their effect upon the person to whom they were said or because of his own recollection of having said them.

Nor should we ignore, before examining the relation of these facts to communicable disease control, the extension of family influence into adolescence and adult life. There are families in which the young child has quite a little of the freedom of a young animal until he reaches adolescence; at this time, however, he experiences a marked degree of control, exerted by his elders in a conscious attempt at parental influence. This does not always produce the result intended, but it is seldom without result of some kind.

The phenomena of chronological and of delayed adolescence may play an important part in the sanatorium patient population. One may observe, on the one hand, the young patient's temporary substitution of doctor and nurse for parents upon whom he has been dependent emotionally as well as economically. Also, one may note the transference to the hospital staff of hostilities which had their origin in the family situation. In the instance of more than one tuberculous and obstreperous young adult, the seeds of his rebellion are far more likely to be found in unskillful management in his home than in the hospital. However, it is the hospital staff which now has to struggle with the result.

Finally, the presence of young children in the home may be a major factor in the response of the patient and of other members of the family. It cannot be news to you that many parents who otherwise might resist hospitalization will accept it for the protection of their children. Yet their anxiety concerning the nutrition, the happiness, or the behavior of children is a frequent cause of restlessness in patients who began by accepting hospitalization. Are we treating

the patient adequately and intelligently if we do not find a practical answer to such anxieties?

Young birds get pushed out of their nests when they are of an age to try their wings, but young humans and even adult humans continue to live with their elders, affecting and being affected by their elder cultures, by like and unlike tastes, preferences and antipathies.

Group influence is so persistent a phenomenon that you may find it exemplified even in the behavior of men at war who, while wholly separated from permanent relationships, share the attitudes, the convictions, the folklore of the squad, the platoon, the company, and the echelon.

There remains still another phase of family interaction for comment. The influence of persons who are in agreement is obvious enough. But many persons do not require agreement in order to be influenced. Some persons rebel throughout their lives at anything which suggests some aversion of their formative years. Not everyone finds the greatest satisfaction of his personality in a state of peace. Some individuals are happiest when in the midst of what seems to the rest of us a lurid brawl. For such experience is to him—or her—merely the free expression of his personality. Nor is it safe to assume that the couple whose "two hearts beat as one" is necessarily any happier than those who are engaged in fairly continuous argument. Argument or conflict may be the means by which some couples find their particular brand of happiness.

In the sanatorium, failure to find particular conditions which afford emotional satisfaction to the individual may furnish major provocation to the patient to leave against medical advice. For example, the patient who has argued about everything since he learned to talk is affronted by the physician whose policy is to tell his patients very little. In this case, the doctor saves his time and his dignity—and loses his patient.

No one can justly accuse the tuberculosis control movement of ignoring the family entirely. For some years, each member of a patient's immediate household has been designated as a "contact". All of us find great joy in a new item of jargon. Here and there these contacts have been X-rayed. To date, not even industrial X-ray has been more productive in finding early tuberculosis. But tuberculosis control agencies, voluntary and official, have not always made the most of this method of case finding. Often, initial zeal for contact-checking has cooled as the novelty of the method has lessened. Seldom have the clear implications of this brief recognition of the family been applied to the total problem of tuberculosis control. It may be that this is a natural consequence of our pernicious habit of exaggerated hopes and exaggerated statements about everything relating to tuberculosis control. From the days of Robert Koch's researches to current developments in bacteriostatic preparations, we have been led all too often to expect the impossible and have as often led others into the same pathetic fallacy.

In our attempt to answer Robert Koch's question about how the bacilli got into the patient, we have over-sold ourselves considerably on the inevitability of familial infection. Certainly, one case comes from another. Certainly, tuber-

culosis often runs in families because the members of a family live closely together and often have maximum opportunity to infect each other. At first this discovery may look like the key to the whole problem. But it falls short of our first expectations for other reasons—as, for example, the fact that some individuals have a sufficient immunological resistance to tolerate dosages of tubercle bacilli without contracting the disease in any serious clinical form. When fine laboratory theory is upset by the facts of life, the health worker displays a fairly universal human tendency if he sets out on the trail of another panacea and at times, tends to neglect contact-checking.

When we have to deal with any type of chronic illness, we may not soundly assume that we can deal successfully with the individual patient alone. To do so betrays a perspective which has been harshly characterized as social illiteracy. In fact, the citizen's wish to find his own disease or not to find it is an attitude far more influenced by the family than by external influences. A fatalistic grandmother who repeats on the average of once a day some such slogan as that what you don't know won't hurt you, or that a lot of folks worry themselves into sickness, frequently wields far more effect on two generations than the most eloquent editorials, the most thoughtfully planned school curricula. Here is a resistance to case-finding and diagnosis having its roots in the family, yet we snip off the top leaves, hoping to influence the individual.

The diagnosis of tuberculosis, when made, affronts a family legend in which the whole vocabulary of respiratory diseases is a vocabulary of epithet. "Consumptive" is, in many minds, far less a diagnostic term than an emotional rejection, an anathema. Have you not known even professional men and women who carried this type of name-calling from their childhood into professional life? Of late, it is a trifle less common for the irritated doctor to call his tormentor scrofulous or richetic. The current trend is to call him a neurotic, neurasthenic, or a psychopathic personality. (The diagnostic accuracy, I suspect, is not better in one instance than in the other.) In the family, the tradition runs: "There never was any consumption in OUR family,"—another proof of the family's genetic and moral superiority.

When the patient believes what his doctor tells him about the evidence in his chest, how long will it take the family to impeach this testimony? How much capacity for belief in scientific diagnosis has the individual whose family has filled his ears from infancy with a contemptuous abuse of the theory and practice of modern medicine? Suppose the family physician, the health officer, and the public health nurse, by tenacious and determined efforts, overcome all of this resistance in the family and get the patient into a sanatorium. The admission of the patient interrupts his opportunities to share his bacilli with his familiars. It interrupts, temporarily, the opportunities of the family to ply the patient with misinformation and ill-considered advice.

What does the sanatorium do and what do the health agencies do to make the most of these interruptions on behalf of the family, the community, and the patient himself? I suggest that in every step of tuberculosis control, the magic key, the key too seldom used, is education. When education misses fire in

disease control, it is usually because the methods, the materials, and the personnel employed are unsuitable to the objective to be accomplished. All human beings are educable to some degree, by some method. Too frequently we underestimate the possibilities of education because we have applied the term too narrowly, or the effort to employ education is so vague as to target, missile, and trajectory as to be foredoomed in advance to failure.

I have attempted to project glimpses of the problems of the tuberculosis family which would disclose both their nature and their variety and complexity. How are we to deal with such problems in tuberculosis control? First, I should say, every worker in the hospital and the health agency needs to observe their importance and influence in aiding or defeating health objectives. But that importance and that influence is so considerable that it warrants the employment of a personnel adequately trained to specialize in the wide range of personal and social problems which obstruct recovery from tuberculosis.

Those of you who are familiar with social work procedures may have noted that that the major portion of this discussion is made up of some of the basic materials in social case work. I have deliberately withheld the label and as deliberately delayed any reference to economic problems in order to emphasize as vigorously as possible what subject matter is actually involved in the training and skills of social work and what bearing it has throughout tuberculosis control.

About eleven years ago an Ohio sanatorium had among its visitors a deputy minister of health from the imperial Japanese Government. It fell to my lot to play guide to this visitor for several days and to point out the details of our efforts to control tuberculosis from diagnosis to recovery in the city of Cincinnati. Our guest was not very much interested in our roentgenology, which was first grade, or our surgery, which was good, or our laboratory methods, which were fair. This seemed strange to me, for in these things we surpassed our neighbors. I was, it seems, overconscious of the defects remaining in our social treatment of the disease—its patients and their families.

In Japan, our visitor told me, they also had X-ray and surgeons and laboratories. What they did *not* have was a tradition or a government willing to consider the economic problems of a family whose breadwinner became tuberculous. When a worker was hospitalized, our informant said, his family starved unless it was fortunate in its relatives. Accordingly, he stated, the avoidance of diagnosis; the substitution of sputum samples from healthy persons; the impersonation by a well relative for a sick worker, were daily incidents. The sick workers stayed on the job until they dropped and in doing so, infected many other contacts. Hence, he said, tuberculosis control in Japan was a dream of the future.

As a nation, we have not dealt with this factor in tuberculosis control much more intelligently than did the Imperial Japanese Government. Some individual communities have done so. But throughout most of the nation, when you name a community with a high death rate from tuberculosis, you have also named a place where the treatment of economic distress lags behind its progress in medical diagnosis and treatment.

The level of public assistance budgets in many cities, counties, and states is



The identification of these factors and their application to the morale and the behavior of the patient and his family are an important part of the preparation and equipment of medical social workers. This practical psychological contribution to successful doctor-patient relationship is a more important contribution to effective therapy than the related item of economic relief.

Hospitals, health services and associations may profit in this instance as in others by the employment of professionally equipped personnel and by utilizing such skill in planning the course of treatment and recovery.

#### SUMARIO

#### *El papel de la Familia en la Lucha Antituberculosa*

Al ser víctima un individuo de tuberculosis clínica, ciertos factores emotivos muy arraigados afectan y a menudo deciden la forma en que comprende o aplica el consejo del médico. La familia a la que pertenece y el ambiente en que vive determinan frecuentemente, en grado considerable, qué clase de enfermo será y si aprovechará en forma máxima o mínima su capacidad latente para resistir la enfermedad. El conocimiento de los antecedentes del sujeto puede explicar la actitud del mismo hacia la dolencia y su tratamiento y facilitar la clave que conduce a su cooperación.

El descubrimiento de dichos factores y su aplicación a la moral y al comportamiento del enfermo y de su familia constituyen parte importante de la preparación y avío de los asistentes médico-sociales. Este aporte psicológico práctico a las relaciones entre doctor y enfermo es de mayor importancia para la terapéutica eficaz que el punto afín del socorro económico.

Los hospitales y servicios y asociaciones de salud pública pueden beneficiarse en este caso, así como en otros, mediante el empleo de personal profesionalmente adiestrado y la utilización de la destreza del mismo al planear el tratamiento y la reposición.



## EDITORIAL

### The Psychology of the Tuberculous Patient

It has been said that<sup>1</sup> "Socrates, returning from the Thracian campaign, praised the wisdom of the physicians of Thrace in their understanding and application of the principle that the body could not be relieved of symptoms, without first curing the mind. He adjured the physicians of Greece to do likewise." Already his contemporary, Hippocrates, was giving careful attention to the influence of the mind over the body as he went about the cure of disease. Broch<sup>2</sup> reports that Virgil, on his death bed, frustrated by cough, hemoptysis, pleurisy and an inferiority complex, had the good sense to embarrass Augustus Caesar's court physician with this question; "Is there any healing at all without magic?" Plato said: "The great error of our day is that physicians separate the soul from the body." The following couplet from the fifteenth century *Regimen Sanitatis* indicates a firm medieval belief in the power of mind over body:

Joy and temperance and repose  
Slam the door on the doctor's nose.

With rare exceptions, the tuberculous patient needs only a wise phthisiotherapist who knows that mind and body are so interdependent that there can be no life when they cease to function as one. The treatment of the disease would be relatively easy if it were not for the patient with all his psychic susceptibilities. Some psychiatrists believe that when labor begins the unborn babe feels the pressure and experiences a psychic reflex which initiates a prenatal anxiety complex. The scope of this discussion is too limited to permit a consideration of the genesis of all psychic conflicts but this one reference indicates that the complete life cycle of the tuberculous patient must be explored.

Conscious of the human organism as an indivisible whole and the necessity of equable balance for adequate living, involuntarily the phthisiotherapist pursues the psychosomatic concept as did Hippocrates of old without being fussed by this high-sounding new term for a time-tried practice.

While discussing this subject it is well to remember that under the stress of modern life it is difficult for us to escape psychic conflicts. Potentially even the best of us are in line for the madhouse. It is well to remember that there is no straight dividing line between sanity and insanity. Even those who think they are on the beam, daily are being dragged back and forth across the imaginary line by their response to conflicting emotional currents.

Sixty-five per cent of the Veterans Administration sick load is in the realm of neuropsychiatry. Some authorities claim that we need 6,500 additional psychiatrists to take care of the nation's mentally sick. No wonder that Day<sup>3</sup>

<sup>1</sup> Strecker, Edward A.: *Fundamentals of Psychiatry*, 4th Edition. J. B. Lippincott Company, 1947.

<sup>2</sup> Broch, Hermann: *The Death of Virgil*—translated by Jean Starr Untermyer, p. 279. Pantheon Books, Inc., 1945.

<sup>3</sup> Day, G.: *Observations on the Psychology of the Tuberculous*. *Lancet*, Nov. 16, 1946.

of Mundesley Sanatorium attributes a large percentage of pulmonary tuberculosis to "dis-ease in their psychological environment." He thinks 30 per cent of the whole sanatorium population are sick in mind and body. On a broad psychosomatic interpretation we can raise the ante to 100 per cent and not go astray.

With mental instability clinging to a vulnerable *soma*, it is not surprising that the imbalance occasioned by disease often leads to disturbing psychic conflicts. As a rule these are not insurmountable and insofar as possible they should be resolved by the patient with the help of the attending physician. When this can be accomplished without the aid of a psychiatrist the patient's interests are not divided between doctors and his confidence not disturbed. To the average patient the suggestion of a psychiatrist in the management of his case would spotlight his mental aberrations and aggravate his psychic conflicts which otherwise he might have resolved in the course of time almost, if not quite, unconsciously. In the patient's life pattern tuberculosis often comes as a great catastrophe, representing a formidable obstacle to a normal existence. He is in need of a physician he can tie to until the storm passes. Often the art of medicine becomes the simple art of being merciful. The assurance of genuine interest and sympathy captures the patient's confidence and secures coöperation. Telling the patient bad news is not easy. It's a poor doctor who precipitates a hurricane and fails to anchor the storm-tossed soul.

No field in the whole realm of medicine offers such exacting, intriguing and stimulating opportunities for service as that encompassing the management of pulmonary tuberculosis. Naturally, tuberculous patients representing a cross section of humanity run the scale from peaches and cream to fire and brimstone.

The physician who hopes successfully to walk the ward and win the respect and confidence of his patients, must tap the seat of reason, appraise the patient's character and carefully analyze his psychic response to disease. To dissipate fear and resolve conflicts he must possess a rare personality with exceptional qualities. If the writer were asked to enumerate these qualities he would name the traits Goethe attributed to Voltaire, but not without self depreciation and apologies to all fellow physicians: "Depth, genius, imagination, taste, reason, sensibility, philosophy, elevation, originality, nature, intellect, fancy, rectitude, facility, flexibility, precision, art, abundance, variety, fertility, warmth, magic, charm, grace, force, an eagle's sweep of vision, vast understanding, rich instruction, excellent tone, urbanity, vivacity, delicacy, correctness, purity, cleanness, elegance, harmony, brilliancy, rapidity, gayety, pathos, sublimity, universality, perfection, indeed behold"—the great physician. Those who are not familiar with the task the physician faces will be impressed with the need of all these qualities as this discussion unfolds.

Often the apparently well poised patient, upon being apprised of the presence of tuberculosis and the necessary therapeutic requirements, may, through the exercise of cultivated inhibitions, artfully conceal mild psychic conflicts. Nevertheless, these emotional upsets may initiate an imbalance resulting in functional disturbances with the possibility of organic changes. The wise physician may anticipate such an eventuality and employ preventive psychotherapy, or, if he

does not immediately sense the psychic difficulties and the patient is not exhibiting satisfactory response to management, he may be able successfully to penetrate the veil of graceful acquiescence and discover existing occult psychic conflicts.

Moderately stable victims of the disease with obvious mild psychic conflicts represent a large percentage of the patient load. With a favorable environment, a skillfully applied educational program and well chosen therapeutic methods, almost without exception their conflicts are resolved and they make good patients.

More emotional and less stable persons, upon being informed of the presence of tuberculosis, may immediately burst into tears, spurning all efforts at reconciliation. In many cases, this distressing complex may be gradually modified through education, replacing exaggerated ideas with consoling facts artfully presented by a sympathetic, far-sighted physician who must at the same time compose distraught relatives.

Occasionally patients stricken with even more serious psychic conflicts seek the protection of silence. These individuals are in dire need of neuropsychiatric help and prompt measures should be directed toward a better understanding of their physical condition, its therapeutic implications and prognostic possibilities. Well planned educational efforts on the part of the attending physician may succeed in making a good soldier of a whimpering coward. Because of hopeless instability of the nervous system in certain patients, the obstacles may be insurmountable and the end hastened by continued anxiety. Fortunately this course is rarely experienced, especially if the attending physician is reasonably competent and exceptionally patient.

The patient's domestic and social situation is very important. For parents, the mental strain of exposing their children by being in contact with them or being separated from them is always a factor influenced by the age, character and temperament of the patient and the children, and by the environmental conditions. Adoring mothers who cherish an abiding sense of sacrificial duty in the home cannot surrender their position without psychic conflicts which may, in some cases, prove a serious handicap. Such difficulties may be overcome by convincing the mother that contact with children should be broken and management graciously accepted in order that she may later safely resume her place in the home. Out of his experience the physician may be able to assure the anxious mother that in all probability her children will be protected physically and benefited psychically by her temporary absence.

Separation of husband and wife may occasionally lead to serious psychic conflicts. Here the range and scope of evil possibilities hinge upon the character and temperament of the respective personalities and their ability to maintain equable social and moral standards under abnormal conditions. There is nothing so discouraging as domestic infelicity, especially when accompanied by an incapacitating disease and the haunting fear of inconstancy. Not infrequently, an irresponsible personality with sharpened psychic susceptibilities may manifest serious conflicts because of imaginary dangers. Such evil fears

spring from groundless illusions which may be aggravated by isolation and physical inactivity. On the other hand, the attending physician occasionally finds an unsuspecting soul "singing at her grinding," suddenly shocked by the deadening consciousness of a faithless spouse. Nothing leaves one so inert, so devoid of psychological competency, so unfit for disciplined battle.

Unmarried lovers may suffer similar conflicts, often magnified by the fact that chronic invalidism may cool the ardor of a coveted lover. Such fears may lead to the precipitate negotiation of matrimony with all the hazards of such an untimely union.

These problems of the heart place upon the attending physician varied responsibilities. Some may be successfully executed through the exercise of ordinary skill, while others may require the wisdom of Solomon. But, with openness of mind and keen observation, the physician learns in the school of life and develops a certain skill in giving more than is demanded by strict measure. Through such giving, tolerance is broadened, understanding enlarged, perception sharpened and initiative finds its appointed course. The exigencies of each case must suggest the method, which will necessarily depend upon "the character of the metal, the heat of the forge and the weight of the hammer."

The resourceful physician, with plenty of time, sincerity of purpose and straightforwardness of action, may succeed in bridging gaping chasms and in healing sensitive wounds of the soul. As may be said of physical scars, psychic scars often memorialize heroic deeds. Such memorials should rest securely among the unheralded satisfactions of both patient and physician.

Obviously the wide range of psychic manifestations makes adequate discussion impossible. The attending physician must be ready to meet the needs of his tuberculous patients as they come from every level of society, psychically geared to this fast-going, highly scientific, mechanistic age in which mankind has modified his religion in favor of the less satisfying guidance of science and reason. When faced with what they consider a serious life hazard, patients, almost without exception, seem to suffer from an obvious sense of personal insufficiency and a need for an abiding faith in some unseen power. No doubt Ibsen had this in mind when one of his characters, under emotional strain, said: "Without a fixed point outside myself, I cannot exist!"

Even un-Christian, self-sufficient Goethe, when threatened with destruction by storm on the rocks of Capri, quieted his terrified fellow passengers by urging them to pray and by reminding them of Christ walking on the water.

Henry C. Link's book, *The Return to Religion*, was inspired by an exhaustive study of psychology as influenced by a long financial depression. He feels that the Bible remains one of the most promising texts for the solution of fundamental psychic conflicts. It is reported that shortly before his death Dr. William J. Mayo said, regardless of what people think of religion he had found that patients with some anchor outside themselves made life much easier for the surgeon.

The wise physician knows that in certain types the religion of Christ and the obstinacy of human frailties may come together with such odds as to create grave psychic conflicts or to aggravate those already existing. Advisedly in

those cases where remorse overwhelms the seat of reason, the physician may venture to cite Mark Twain's opinion of conscience, "Your conscience is a nuisance. A conscience is like a child. If you pet it and play with it and let it have everything that it wants, it becomes spoiled and intrudes on all your amusements and most of your griefs. Treat your conscience as you would treat anything else. When it is rebellious, spank it—be severe with it, argue with it, prevent it from coming to play with you at all hours, and you will secure a good conscience; that is to say, a properly trained one. A spoiled one simply destroys all the pleasure in life."

A broad knowledge of nature, literature, history and biography will better enable the physician to interpret his patient's psychic needs and to direct his reading along lines psychically helpful. Often the most essential initial educational adventure is teaching the patient the plain truth about tuberculosis. The story in language he can understand is often a source of great comfort and seldom is it wholly discouraging. Rarely is a patient's condition so serious as to preclude the possibility of a ray of hope. But, in many patients the truth should be given in graduated doses, never exceeding his psychic tolerance. It is well to remember there is no swift approach, no short cut, no possibility of sudden arrival.

The more nervous and fearful the patient, the more important the sanatorium becomes in the management. The daily contact with physicians, nurses and other patients in a well ordered sanatorium serves as a revelation, inspires confidence, increases knowledge and dissipates fear, thereby creating the best possible conditions for progressive improvement. For many there is nothing more hopeless than to lie down at home with the shocking consciousness of the intimate presence of a dread disease, fully aware of the partially concealed anxiety of poorly informed, sympathetic loved ones, obviously ignorant of the patient's most urgent needs. Genuine poverty and the necessary household penury often serve as aggravating factors. Such an environment encourages dangerous introversion and may cause the patient silently to hug his own burden of bitterness through long days and nights, tortured with a hopeless sense of fear and uncertainty and possibly harboring the spirit of rebellion so common in the course of a great catastrophe.

A misplaced word may cause a great deal of unnecessary worry. A passing remark of a friend or another patient may result in a wakeful night or days of useless anxiety. The educational program and the daily routine should be designed to prevent or to meet such psychic events. Through the patient application of the attending physician or the well trained public health nurse, the acquisition of knowledge and understanding on the part of the patient may replace doubt, fear and rebellion, with hope and its attendant virtues.

The physician who loves people and has the gift of getting on with his patients can penetrate the well planned defenses of the shrewdest pachyderm. There is a rich reward in the pursuit and discovery of that spark of response hidden beneath the crust of certain reserved personalities. This spark may be fanned into a warm glow of great mutual value. Confidences are to be treasured not

only as evidence of therapeutic success but because they open avenues through which curative suggestions may travel to their coveted goal.

The physician who does not gain access to the sacred precincts hidden beneath his patient's calvarium is missing one of the most fascinating functions of the patient-physician relationship. He is forfeiting the opportunity to harness the energy which generates the storms of frustration and motivates behavior and thereby he is sacrificing a vital therapeutic force.

Through proper education the patient must be directed toward self-expression and the execution of enlightened responsibility. As far as possible the physician should impress upon him the importance of a partnership in the difficult task of getting well. It should be understood that this happy union cannot give birth to good health without mutual participation in a courageous campaign. Early in the course of treatment he should be impressed with the fact that both mind and body must be wholly committed to the task of getting well and that there should be no respite. Finally, he must learn with Carlyle that "the duty of being brave is an everlasting duty", even though it may lead to the last great mystery.

LEWIS J. MOORMAN



Max Pinner  
1891-1948

## Max Pinner

November 28, 1891–January 7, 1948

In the death of Dr. Max Pinner on January 7, 1948, the country has lost one of its keenest minds and greatest contributors to knowledge in the field of tuberculosis and diseases of the chest. He was born in Berlin, Germany, November 28, 1891, and his early education was secured in Switzerland. After other studies in Germany he served in the Medical Corps of the German Army from 1915 to 1919. A doctorate in medicine was granted him in 1920 at the University of Tübingen.

Doctor Pinner's interest in tuberculosis was begun during his medical studies when for a time he was associated with Professor Much, whose researches in the bacteriology of tuberculosis are well known. As the young physician was not satisfied with conditions in Germany, he determined to come to America, which he did in 1920. He went directly to California, where for a time he served on the staff of a private sanatorium. While there he met Miss Berna Rudovic, whom he married March 1, 1924, and who survives him. Soon after their marriage they went to Chicago, where Doctor Pinner joined the staff of the laboratories of the Municipal Tuberculosis Sanitarium. The interest and assistance which Mrs. Pinner gave her husband, particularly in his writing and editorial work through the years, were credited by him as contributing much to his success.

In 1926 he came to the William H. Maybury Sanatorium at Northville, Michigan, as pathologist and director of the laboratories. His interest in tuberculosis had led him to become a great admirer of Dr. Allen K. Krause. The latter was editor of the *American Review of Tuberculosis* during this period and was at the height of his brilliant career as author, research worker, and teacher. Doctor Krause had left Johns Hopkins University to head the Desert Sanatorium at Tucson, Arizona, and having developed an appreciation of the splendid talents possessed by Max Pinner, invited him to join the staff at the new institution, where for several years the two friends worked together. At this time, Doctor Pinner began his connection with the *American Review of Tuberculosis* through assisting Doctor Krause. In 1937, Doctor Pinner was made Associate Editor and because of the illness of Doctor Krause, took over most of the responsibility for the editorship. In 1941, Doctor Pinner was made full editor, in which capacity he continued up to the time of his death. In 1935, he became principal pathologist for the tuberculosis hospitals of the New York Department of Health, and organized the splendid laboratory service for the newly opened state sanatoriums.

Throughout all of Doctor Pinner's work he never became a purely laboratory research man but always maintained his interest and skills in the clinical side of diseases of the chest. Thus, it was quite natural that he should be chosen as chief of the chest service of Montefiore Hospital in New York and Medical Director of the affiliated sanatorium at Bedford Hills in 1938. In this position he succeeded to the post formerly held by an illustrious predecessor, Dr. Maurice



Fishberg. At that time, Doctor Pinner was also appointed to the faculty of Columbia University, College of Physicians and Surgeons, and reached the rank of clinical professor of medicine.

In 1946, ill health forced him to resign from active work at Montefiore and Columbia, and he retired to California. He and his wife located in Berkeley, where he continued to edit the American Review of Tuberculosis, carry on some other writing and act as consultant to the Veterans Administration.

Doctor Pinner was active in a number of special professional societies, being a Fellow of the American College of Physicians, a member of the Society for Experimental Biology and Medicine, the American Association of Pathologists and Bacteriologists, the American Association for Thoracic Surgery, and the American Trudeau Society.

In recognition of his many contributions to our knowledge of tuberculosis, the National Tuberculosis Association honored him and honored itself by awarding him the Trudeau Medal in 1946.

There were many phases of tuberculosis that came under the searching study of Max Pinner. Some of his more important studies dealt with: methods for detecting tubercle bacilli and their differentiation from other acid fast organisms; the genesis of the pulmonary lesions of tuberculosis based on extensive observations of untreated lesions; the correlation of clinical observations with post mortem findings in establishing the development and progress of the disease and the acute subapical lesion and its relation to the beginnings of symptomatic disease.

Doctor Pinner was intrigued by the problem of the severity of tuberculosis in the Negro as compared with the disease in the white. His extensive post mortem studies revealed the greater tendency to exudative response in the Negro and the greater frequency of hematogenous spread of the infection which occurred in this race. He emphasized that the duration of the disease from onset of symptoms to fatal terminus was usually only one-half as long in the Negro as in members of the white race.

Noncaseating tuberculosis was proposed by him as an explanation of the nature of sarcoidosis. He marshalled much evidence to support this view although he admitted readily that he had not been able to prove the concept to be correct beyond any doubt.

His observations of the formation and the healing of cavities in pulmonary tuberculosis added much to the better understanding of these phenomena.

The evaluation of various therapeutic methods in the field of chemotherapy and in collapse therapy was greatly aided by his combined approach from the standpoint of the clinician and pathologist.

Of Doctor Pinner's many writings probably his most outstanding work was the book, "Pulmonary Tuberculosis in the Adult." Here we have scientific writing at its best. In the words of the author, "The primary aim of this book is not to impart knowledge but to create understanding..." What better keynote to the whole life and work of Max Pinner could there be than this! His many associates will always remember his great ability to grasp the meat of a subject, weigh it and place a true value upon it. His ability to map out a course

of study, an experiment or some other approach to clarifying an important point was most remarkable. Above all, he was intellectually honest and abhorred that which was artificial and shallow.

Many physicians can look back with gratitude to the stimulus given them through association with Doctor Pinner; stimulus which prompted them to be more than just routine persons but rather individuals who find zest and satisfaction in tackling unanswered questions and making a contribution not merely to knowledge but to understanding.

Not in the least outranked by his ability and attainment in the scientific field was his capacity for friendship with his associates both in and out of professional circles and for loyalty to his family.

His memory will be cherished by his numerous friends and by the many who knew him only through his writings.

BURCE H. DOUGLAS, M.D.

March 21, 1948



*Blackstone Studios, Inc., 20 West 57th St., New York*  
Wm. Charles White  
1874-1947

## Wm. Charles White 1874-1947

Dr. Wm. Charles White, for a quarter of a century chairman of the Committee on Medical Research of the National Tuberculosis Association, died at the home of his daughter near Washington, D. C., on August 10, 1947 at the age of 72 years. He was active in the antituberculosis movement for more than forty years, and one of the last of the tuberculosis specialists trained by the earliest leaders of the tuberculosis control program, Osler, Welch and Trudeau.

Dr. White was born on September 3, 1874, in Woodstock, Ontario, of parents of predominantly Scottish ancestry, and attended the Woodstock public schools. He received the M.B. degree from Toronto in 1898, and the M.D. in 1902. In 1901, after post-graduate study in pathology in Leipzig and Heidelberg, and on the recommendation of Osler, on whose wards he had served during vacation periods after his graduation in medicine, he accepted the position of professor of pathology at the Central College of Physicians and Surgeons in Indianapolis. He was also professor of neuroanatomy and clinical psychiatry in the School of Medicine of the University of Indiana. In the midst of his work he discovered that his sputum was, as his laboratory assistant said, "swimming with t.b." He terminated his program, returned to Canada to secure advice from his friends Dr. Jabez Elliot and Dr. Charles D. Parsitt, and later went to the Trudeau Sanatorium.

Within a few months he was able to return to work. At that time the newly formed Tuberculosis League of Pittsburgh was in need of a medical director. The President, Mr. Otis Childs, wrote to Dr. Trudeau for advice. Dr. White was recommended for the position, and the Board waited until he was able to leave Trudeau and assume it.

Tragic as it was to desert his promising work in Indiana, the seeming misfortune set the course for a future highly productive professional life in a new field. The short period of treatment required to arrest his tuberculosis had actually added greatly to his scientific background. In Pittsburgh, Henry Phipps, Andrew Mellon, R. B. Mellon and others provided money and facilities for the new program. Association with these outstanding industrial leaders gave Dr. White an insight into the dominant role of industry in research, and guided him in future contacts and associations. He served also as Associate Professor of Medicine in the University of Pittsburgh. The breadth of his interest is indicated by the diversity of subject in his published papers, which ranged from laboratory studies on tuberculosis to investigations on the effects of smoke on health, and tuberculosis as a social problem. During these years he was increasingly active and influential as a member of the Board of Directors of the National Tuberculosis Association.

In 1917 his duties in Pittsburgh were sharply interrupted by the entrance of the United States into the conflict that had been raging for three years in Europe. Dr. White went to Europe in the service of a private organization in Paris, known

as the "Tuberculeux de la Guerre," and was later appointed Chief of the Bureau of Tuberculosis of the American Red Cross. The work of these groups was later extended to Italy. For his services in Europe he was decorated with the Serbian order of St. Sava and the Commandatore of the Order of the Crown in Italy.

Shortly after the war, as a representative of the National Tuberculosis Association, in company with Dr. Charles J. Hatfield and Dr. David R. Lyman, he took part in conferences in London and Paris which led to the organization of the International Union Against Tuberculosis.

On his return from Europe in 1919, Dr. White resumed his position in Pittsburgh as medical director of the Tuberculosis League and the associated R. B. Mellon Research Laboratory. His interests, however, were now less than ever local, and he was soon more deeply concerned with national health problems. The care of veterans from World War I proved an enormous problem, and the need for rapid expansion of facilities was urgent. Congress placed the program of hospital construction under the direction of the Secretary of the Treasury, Andrew W. Mellon. Mr. Mellon requested Dr. White to assume the chairmanship of a committee of consultants with responsibility for selection of sites and construction of hospitals for veterans. Dr. White traveled extensively in the discharge of his duties. The service was not an entirely peaceful one. Relations among the various federal agencies for the care of the veterans were intricate. The services of this committee led to the establishment of eighteen veterans hospitals.

In 1920 Dr. White was made chairman of the new Committee on Medical Research of the National Tuberculosis Association, formed during the presidency of Gerald Webb. In 1923 he left Pittsburgh, to act as consultant to the U. S. Public Health Service under Secretary of the Treasury Andrew Mellon and Surgeon General Hugh Cumming.

His position in Washington proved of great importance in his new responsibility in the National Tuberculosis Association. It broadened the scope of his contacts, which were reflected later in a mutually profitable coordination of the research and control programs of the National Association and the U. S. Public Health Service. The history of the Committee on Medical Research has been well covered by Dr. White's daughter, Dorothy White Nicolson, who was his able secretary from 1924 until his retirement in 1946, in "Twenty Years of Medical Research," a publication of the National Tuberculosis Association.<sup>1</sup> The budget of this committee increased from \$500 in the beginning to more than \$50,000 at the time of his retirement.

Of all Dr. White's achievements the most outstanding was his development of the research program of the Association. He had a passion for basic research and coöperation. He was convinced that clinical investigators could be trusted to continue without specific assistance in the application of known facts in the therapy of tuberculosis, and the improvement of medical and surgical procedures. In the last analysis, however, he felt that basic laboratory research was essential to continued progress, and that this should be focused on the fundamental

<sup>1</sup> I am indebted to Mrs. Nicolson for much of the material in these paragraphs.

relationships between the tubercle bacillus and the body's monocytes and other phagocytic cells. He insisted that these relationships must be fundamentally chemical, that the changes produced in tissues invaded by tubercle bacilli must be in essence the result of chemical stimuli from products of the bacillus itself, and that in the long run a specific therapy for tuberculosis should result from an understanding of the changes brought about by these stimuli. These views led to grants for research on tuberculosis to a group of specialists in the basic medical sciences, and thus united in tuberculosis research the skills of anatomists, biologists, bacteriologists, chemists and physiologists who otherwise might never have been attracted into the field of tuberculosis. Throughout his long service he maintained an active correspondence with each of these investigators, visiting them in their laboratories whenever possible, bringing them together in annual meetings, and stimulating their coöperation by personal contact and participation in conferences. In later years various clinical investigations were coordinated with the laboratory studies of the Committee on Medical Research, and an extensive program was maintained for the improvement of clinical roentgenology.

In his long years as Chairman of the Committee on Medical Research he inspired many young investigators and developed them for positions of influence, a service as valuable as the work of the Committee itself. These men, in turn, have brought in others, and work commenced at universities throughout the country has led to new investigations here and abroad, and the establishment of a school of thought on the chemistry and pathology of tuberculosis.

In one field, then only slightly explored, he was ahead of his time, viz., the relation of soil organisms to the tubercle bacillus. The possibility of significant relationships attracted Dr. White, and it is of interest to note that, on his recommendation, a grant for studies of the fate of tubercle bacilli in soil was made by the Committee on Soil Microbiology of the National Research Council to the laboratories at Rutgers University and the New Jersey Agricultural Experiment Station where streptomycin was later discovered. Dr. White was chairman of this committee and Dr. Selman Waksman a member.

Dr. White's medical interests were by no means confined to tuberculosis. Next to the National Tuberculosis Association and the U. S. Public Health Service, he was most concerned with the work of the National Research Council. In 1928 he was elected Chairman of the Division of Medical Sciences of this body, and after finishing his term in this office he undertook the direction of the Council's Committee on Drug Addiction, the objective of which was to discover a drug or drugs with the pharmacological properties of morphine, but without its habit-inducing effects. This Committee established an organic chemical laboratory in the National Institute of Health which synthesized numerous morphine substitutes that approached, if they did not reach, this goal.

Even these positions did not exhaust his medical interest and curiosity, nor take up all of his time. At various periods he found the time and strength for important committee work on syphilis, cancer and other diseases. He was a valuable member of the local health organizations of his home city, Washington,

and was President of the District of Columbia Tuberculosis Association and Chairman of the Advisory Health Committee of the District of Columbia Health Department, bringing to the one the service of the other, and with tact and personal charm ensuring effective coöperation in the face of the difficulties inherent in organizations subject to all the political pressures of the nation's capitol. He was also a member of the Board of the Warwick Memorial Cancer Clinic, and a charter member of the District of Columbia Cancer Society.

His medical society affiliations were numerous, including the Association of American Physicians, the American Clinical and Climatological Association, the American Sanatorium Association, the American Trudeau Society, the American Association of the History of Medicine, the American Association for the Advancement of Science, the New York Academy of Medicine and the Academy of Medicine of Washington, D. C. He was a member of the Advisory Councils of the Milbank Memorial Fund and the Henry Phipps Institute. An honor testifying to the high esteem in which he was held in Washington was the Presidency of the Cosmos Club, a Washington social club for men in professional life, well known throughout the United States.

Dr. White was a constant reader, well informed on the nation's affairs, with a wide acquaintance among leaders in national life in Washington. He had a keen sense of humor, always evident in an unusually happy home life. He and Mrs. White, the former Mary Ellen Cameron of Toronto, Ontario, were charming hosts to the hundreds of friends and professional colleagues who visited them in their home. Mrs. White died in 1945, a blow from which Dr. White, already in failing health, never recovered. They are survived by two daughters, Dorothy Cameron, now Mrs. Hugh T. Nicolson of Westmoreland Hills, Maryland, and Mary Veitch, now Mrs. William C. Goodwyn of Louisville, Kentucky.

ESMOND R. LONG

## AMERICAN TRUDEAU SOCIETY

### Present Policy of the American Trudeau Society on BCG Vaccination

#### *Committee on Chemotherapy*

H. McLeod Riggins, M.D., *Chairman*

J. Burns Amberson, M.D.

Emil Bogen, M.D.

Paul A. Bunn, M.D.

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Kirby S. Howlett, Jr., M.D.

Walsh McDermott, M.D.

Edward N. Packard, M.D.

Carroll E. Palmer, M.D.

Arthur M. Walker, M.D.

#### *Laboratory Subcommittee on Chemotherapy*

Guy P. Youmans, M.D., *Chairman*

H. Corwin Hinshaw, M.D.

William Steenken, Jr.

C. Eugene Woodruff, M.D.

The members of the Society and other physicians in the United States have been interested for many years in the active immunization against tuberculosis with BCG. The expansion of public health activities in the field of tuberculosis control by official and voluntary agencies and the acquisition of new knowledge concerning immunity in tuberculosis have prompted the Society to make the following observations and recommendations:

- I. BCG vaccine, prepared under ideal conditions and administered to tuberculin negative persons by approved techniques, can be considered harmless.
- II. The degree of protection reported following vaccination is by no means complete nor is the duration of induced relative immunity permanent or predictable. The need for further basic research on the problem of artificial immunization against tuberculosis is recognized and is to be emphasized. Studies should be directed: (a) toward the improvement of the immunizing agent, (b) to the development of criteria for vaccination and re-vaccination and (c) to determine more accurately which groups in the general population should be vaccinated. Several well controlled studies are underway at the present time and it is expected that others will begin within the near future.
- III. On the basis of studies reported in the European and American literature, an appreciable reduction in the incidence of clinical tuberculosis may be anticipated when certain groups of people who are likely to develop tuberculosis because of unusual exposure, inferior resistance, or both, are vaccinated.
  - A. In the light of present knowledge vaccination of the following more vulnerable groups of individuals is recommended provided they do not react to adequate tuberculin tests.



1. Doctors, medical students and nurses who are exposed to infectious tuberculosis.
  2. All hospital and laboratory personnel whose work exposes them to contact with the bacillus of tuberculosis.
  3. Individuals who are unavoidably exposed to infectious tuberculosis in the home.
  4. Patients and employees of mental hospitals, prisons and other custodial institutions in whom the incidence of tuberculosis is known to be high.
  5. Children and certain adults considered to have inferior resistance and living in communities in which the tuberculosis mortality rate is unusually high.
- B. Vaccination of the general population is *not* recommended at this time except for carefully controlled investigative programs, which, as a rule, will be best carried out under the auspices of official agencies such as the U. S. Public Health Service, state and municipal health departments and other especially qualified groups.
- IV. BCG vaccine should not be made available for general distribution in the United States at this time because: (a) the most effective strain of BCG has not been agreed upon nor has fully satisfactory standardization of the vaccine been achieved, (b) the best qualified experts have not agreed as to the most effective method of vaccination and (c) fully satisfactory arrangements have not been perfected for transportation and storage of the vaccine.
- The vaccine should be prepared only in accredited laboratories especially devoted to this task, in which virulent tubercle bacilli are not cultivated or handled and in which all other possible precautions are exercised to assure safety and quality of the product.
- Adequate record systems should be devised for management of the statistical problems involved in recording and following large numbers of vaccinated people. These and other problems of particular importance are now being studied on an extensive scale by official and voluntary agencies in the United States and in close collaboration with European scientists experienced in this field.
- V. The Society believes that since BCG vaccination affords only incomplete rather than absolute protection, the most effective methods of controlling tuberculosis in the general population are (a) further improvement of living conditions and the general health, (b) reduction of tuberculous infection, which can be accomplished by modern public health methods and the unremitting search among presumably healthy individuals for patients with infectious tuberculosis, (c) prompt and adequate medical and surgical treatment of patients with active disease, (d) segregation and custodial care of those not amenable to accepted forms of therapy and (e) adequate rehabilitation.

Fortunately, great advances have been achieved during recent years in the

development of diagnostic methods applicable on a mass scale and there have been significant improvements in the surgical and medical treatment of tuberculosis. The expansion of modern diagnostic, therapeutic and rehabilitation facilities is required at this time to make full use of these new methods which can accomplish further dramatic reduction of tuberculosis mortality and morbidity rates in the United States.

It is to be emphasized that BCG vaccination must not be regarded as a substitute for approved hygienic measures or for public health practices designed to prevent or minimize tuberculous infection and disease. Vaccination should be regarded as only one of many procedures to be used in tuberculosis control. Vaccination seems unwarranted: (a) in areas in which the tuberculosis mortality rate is extremely low and (b) in localities in which the tuberculin test is of especial value as a differential diagnostic procedure.



# THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

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**Working Capacity of the Healed Tuberculosis Patient.**—Funds devoted to vocational guidance of recovered tuberculosis patients are a legitimate and wise investment. Readaptation should begin before recovery is complete in order to bring about gradually the necessary readjustments or even a change of occupation, however hard the latter may prove. In Argentina only a few and circumscribed attempts have been made in this direction, such as Cetrángolo's at the Santa María Sanatorium and the National Central Hospital. Nores at Our Lady of Mercy Hospital combines treatment with training in weaving and through private coöperation has opened a 22-bed pavilion for healed women patients. The late Raimondi was one of the pioneers in this campaign. Poultry raising seems an ideal occupation for patients on the way to recovery or already recovered as the work required is comparatively easy and not hard to learn, the market is ready at hand and the business may be undertaken on an individual small scale. It might even be possible to open at some sanatoria aviculture schools with enrollments of about 100 students. —*Capacidad laborativa del tuberculoso recuperado*, J. F. Verna, S. A. Sarmiento, J. G. Rodríguez & B. Perrier, *Arch. de Secretaría de Salud Púb. Nac.*, January, 1947, 1: 31.—(A. A. Moll)

**Occupational Tuberculosis.**—The concept of tuberculosis as an occupational disease has been gradually gaining in acceptance in the United States. In Peru the only provisions made by law for occupational disease apply to pneumoconiosis or any other disease ac-

quired at work through intoxication with gases derived from chemical products. X-ray surveys of workers in various industries in Peru revealed the following regarding the incidence of tuberculosis (the first percentage indicates clinically active disease, the second, suspicious): shoe factories, of 924, 3.46 per cent, 1.19 per cent; textile mills, of 1,522, 2.03 per cent, 1.90 per cent; glass manufacture, of 316, 1.89 per cent, 1.89 per cent; pharmaceutical products, of 356, 3.94 per cent, 1.92 per cent; dairy farms, of 197, 1.01 per cent, 3.04 per cent. In order to arrive at a proper scientific evaluation of tuberculosis as an occupational disease, the following steps are considered necessary: (1) intensification of X-ray surveys with more emphasis on the type of work performed by the individuals examined; (2) international accord on methods of social investigation with a view to analysis of possible determinative factors, with remedial legislation in mind; (3) accord on occupational nomenclature. The occupational nature of tuberculosis, from the legal point of view, in people working with tuberculous patients is undeniable, and should be so recognized.—*Datos sobre tuberculosis ocupacional*, O. Garcia Rosell, *Rev. de tuberc. de Peru*, January-June, 1947, 24: 971.—(F. Perez-Pina)

**Tuberculo-pneumoconiosis of Coal Miners in Belgium.**—The author limits his paper to a discussion of X-ray examinations made during his service at an antituberculosis dispensary in a mining district in Belgium (Mons). About 90 per cent of the miners were exposed to rock dust containing silica.

Reproductions of twenty-four typical X-ray films accompany the paper. In the early stages of silicosis, the shadows of the lungs have a finely granular or granite-like quality which is produced by the intersections of a very fine network of fibrous strands. At this stage there are few symptoms or physical signs. A little later these nodules are larger and distributed symmetrically in the central areas of the two lungs. Such radiological findings are typical of uncomplicated silicosis and are rarely accompanied by symptoms. They are accidentally met with in the course of surveys when the entire group of miners is examined. After a time, in infected cases, shadows appear which indicate the presence of a tuberculous element. As described by Courtois, they consist, in closed cases, of the development on the granular background of (a) trabeculo-nodular opacities which are more evident at one or both of the apices, (b) of lines indicating inflammation of the interlobar or lobar pleura, (c) of limited unilateral clouding, and (d) of an appearance suggesting migration and coalescence of the nodules in certain parts of the lung which are designated by Courtois as centres of attraction. In open cases of tuberculo-pneumoconiosis there are, in addition, limited honeycombed areas and other indications of cavitation. Finally, indications of retraction of the lung and of compensatory emphysema appear, which are often adjacent to the cloud-like or honeycombed areas. Deviation of the trachea occurs, tenting of the diaphragm, and further breaking down of adjacent lung tissue. The heart in young subjects is hypertrophied and the aorta becomes tortuous and elongated. In other cases the development is different and, instead of a somewhat granular and disseminated nodular appearance followed by concentration and breaking down of coalescing areas of nodulation, there seem to develop large pseudo-tumorlike masses. Such shadows may be found in silicosis without tuberculosis, and are then usually central. When tuberculosis is added, they are apt to be less symmetrical and to be found also at the apex or base, and to be accompanied with the other

indications of tuberculosis already listed. Tuberculosis has been twice as frequent among the miners in Belgium, especially in workers over 40, as it has been among other laborers. The present underfed and exhausted state of many miners indicates probable increase in the number of open cases. Most of the miners work in hard rock, but even those who have not apparently been as directly exposed to silica dust develop some silicosis, possibly from siliceous dust which has settled in the bottom of the mine. Some of these men have previously worked in other mines where they have been directly exposed to silica. Compensation should be available for silicosis developing in workers in any of the mines.—*Considerations radio-cliniques sur la tuberculopneumoconiose des houillcurs*, A. Joucol, *Rev. belge de tuberc.*, 1947, No. 2, 97.—(A. T. Laird)

**Quiescent Pulmonary Tuberculosis.**—The author pleads for more exacting standards in assessing the "quiescent" case of pulmonary tuberculosis. In the no-sputum case, one should try to obtain material by laryngeal swab, gastric lavage or pulmonary lavage. The laryngeal swab is preferred in a busy clinic. In 152 cases with no sputum, laryngeal swab gave 34 positive results. In 32 cases, all three procedures were used; in 5 of these, positive results were obtained by all three methods. One was positive on pulmonary lavage alone and 2 on laryngeal swab alone. One was positive on both gastric and pulmonary lavage. Negative results by all methods were obtained in 23 cases. Pulmonary lavage is the only method in which smears are reliable; in the others, cultures are necessary.—*The "Quiescent" Case of Pulmonary Tuberculosis*, J. Cuthbert, *Tubercle*, October, 1947, 28: 211.—(A. G. Cohen)

**Tuberculous Pleural Effusion.**—In a series of 233 patients with pleural effusion seen from 1935 to 1944, 40 had pulmonary tuberculosis on initial examination. The lesions were classified as minimal in 16, moderately advanced in 19 and far advanced in 5 cases.

The type of lesion was fibroid in 20 (6), fibro-calcific in 8 (1), nodular in 3, fibrocascous in 6 (5), caseous pneumonie in 2 and miliary in one (1); the numbers with positive sputum are indicated in parentheses. No collapse therapy was given. The patients were followed until 1946; by then 5 had died, 34 were alive and one was lost to observation. Of the living patients, 7 had active pulmonary tuberculosis. Pleural effusion in chronic pulmonary tuberculosis is not rare. Its onset is not correlated with any particular trend in the disease and the effusion often strikes an apparently well patient. Often there are few symptoms.—*Secondary Pleurisy with Effusion in Pulmonary Tuberculosis*, B. C. Thompson, *Tubercle*, November, 1947, 28: 229.—(A. G. Cohen)

**Hematogenous Tuberculosis.**—Localized hematogenous spread in pulmonary tuberculosis often shows a tendency to spontaneous healing by resolution, calcification and fibrosis. Healing may take place within six months and is determined by disappearance of the roentgenological manifestations and when numerous sputum tests have been found to be negative.—*Spontaneous Healing of Localized Hematogenous Spread in Pulmonary Tuberculosis*, L. Dunner, *Am. J. Roentgenol.*, September, 1947, 58: 283.—(J. E. Farber)

**Primary Thoracoplasty versus Pneumothorax.**—Fundamentally, the indications for thoracoplasty and for pneumothorax are the same. The types of lesions amenable to both types of treatment are identical, with the exception of caseous pneumonia, in which a pneumothorax is indicated and a thoracoplasty contraindicated. Other factors which may contraindicate thoracoplasty, but may permit attempted pneumothorax, are dyspnea, fever, tachycardia, cyanosis, heart disease, renal disease, diabetes, and extrapulmonary tuberculosis. However, some cases with dyspnea, cyanosis and tachycardia due to mediastinal shift produced by the tuberculous process may improve following correction by a thoracoplasty. The mortality in thoraco-

plasty ranges between 7 and 11 per cent. This is no higher than that of similar cases treated with pneumothorax with the known incidence of complications of the latter. In 200 cases treated by thoracoplasty there were 85 per cent cured and inactive among those followed for one to two years, and 75 per cent among those observed for two to three years. These percentages refer to clinical, X-ray and bacteriological cures. Among cases of pneumothorax with the same type of lesions observed for an average of three years, good results were obtained in only 58 per cent. Economically, primary thoracoplasty reduces the length of sanatorium care required. A higher proportion of patients reach the surgeon in better general condition, with consequent reduction in operative mortality figures and with optimal long-range results.—*La toracoplastia precoz, sustitutiva del neumothorax*, A. Percera, *Rev. españ. de tuberc.*, July, 1947, 16: 551.—(F. Perez-Pina)

**Spirography in Collapse Therapy.**—Spirographic measurements were made on individuals before and after subjection to various collapse measures. The results were expressed as percentages of the expected normal for each height as previously determined for Spaniards. With intrapleural pneumothorax there was a reduction of 20 to 45 per cent in vital capacity, mostly in the complementary air fraction, with some diminution in almost all of the other values. After phrenic nerve interruption there was a reduction of about 30 per cent in the corresponding values, which was proportionally less if the function of the base had been previously reduced by pleural thickening. Thoracoplasty resulted in a diminution of 14 to 25 per cent in the vital capacity, with significant reduction of the complementary air fraction. The other respiratory indices were also reduced. In extrapleural pneumothorax there were minimal alterations of all the values, with improvement in some of them.—*Consideraciones espirográficas sobre los procedimientos colapsotérapicos*, J. Codina Suñe, J. Gonzalez-Quijano

& G. de la Peña, *Rev. españ. de tuberc.*, June, 1947, 16: 478.—(F. Perez-Pina)

**Thoracoplasty.**—One hundred cases are reported. These were done at the sanatorium de Seyssuel near Vienne in the department of Isere in France, by Dr. J. de Rougement, from April, 1942 to October, 1945. Many of the patients had been discharged as hopeless from sanatoria in the Alps or Jura mountains, and had been sent back to the plain to die. The authors believe a considerable portion should have been discharged earlier to get the benefit of operative treatment. The results are tabulated as follows: cured, 63; improved, 20; stationary, 1; failed, 2; operative deaths, 9; secondary mortality 5 per cent. They consider as "cured" all cases which showed effacement of lesions radiographically and constantly negative sputum. Five patients have since gone through pregnancy without relapse. All of the thoracoplasties were done with the patient in the sitting posture, with ether or Evipan as the basic general anesthetic. However, Rougement prefers local anesthesia and expects to use it more in the future. The sitting posture of the patient, he believes, offers several advantages. Anemia of the operative field as an indication of impending shock is more readily noted. Hemostasis is easier. Apicolysis when indicated is more readily done because of better visibility. Resections of ribs, especially of the first, are simplified. Vascular accidents are not more frequent. Rather long sections of the ribs were removed, never less than 90 cm. in five ribs, usually about 100 cm., and in one case 141 cm. for six ribs. The first rib was always entirely removed. Care was taken to repair any openings into the pleural cavity with muscle tissue from the corresponding intercostal space in order to prevent drainage into it of any blood of extrapleural origin. After the rib sections have been removed, the question of apicolysis arises. Rougement has used the Semb technique but considers that the maneuver is often difficult and has abandoned it. He does not employ any apicolysis (1) if it prolongs the operation too much, (2) if the

pulmonary lesions are too extensive or too superficial, (3) if there is too much fibrosis, (4) if the pulmonary settling is sufficient without it. The authors classify indications for thoracoplasty as: (1) Typical indications in cases in which the lesion is limited, there is a retractile tendency, the opposite side is satisfactory and the general condition is good. (2) Relative indications, present in cases in which there are more or less serious complications. (3) Salvage indications, the operation being done as a last resort in desperate cases. (4) Pleuro-pulmonary cases, that is, cases of purulent pleurisy with underlying pulmonary lesions, nearly always active. (5) Elective thoracoplasties for basal lesions, of which the authors report 3 that were unsuccessful. Cases where indications for operation were favorable gave 90 per cent cures. Where operation was a last resort, 50 per cent were cured and 30 per cent were aggravated or died, with an operative mortality of 17 per cent. With pleuro-pulmonary indications, 70 per cent were cured.—*Cent cas de thoracoplasties en sanatorium de plaine*, L. Meyer & J. de Rougement, *Le Poumon*, May-June, 1947, 3: 185.—(A. T. Laird)

**Apical Thoracoplasty.**—Apical thoracoplasty in a series of 70 patients has been found to produce effective cures in 42 cases after a minimum of three years follow-up. Of the 70 patients, 80 per cent had cavities above the second costal cartilage, ranging in size from three to more than six centimeters. Contralateral lesions were present in 35 of the patients, although in most cases the process was thought to be inactive. One-stage removal of three to five ribs, with apicolysis in 51 of the cases, was the procedure employed in this series with a postoperative mortality rate of 5.7 per cent. Follow-up studies were made in all cases for at least three years after surgery. Healthy patients comprised 60 per cent of the original series (75 per cent of the surviving patients), with roentgenological evidence of stationary lesions, no cavities and no new spreads, negative sputum cultures and/or negative gastric cultures and no com-

plications such as dyspnea, fistulae, etc. All other surviving patients, of which there were 13, were considered to be ill. In general, best results were obtained in those patients having the smallest cavities and no contralateral disease.—*The Permanent Results of Apical Thoracoplasty*, Hagn-Meincke, *Acta tuberc. Scandinav.*, 1947, 21: 190.—(P. Q. Edwards)

**Internal Pneumonolysis.**—Thoracoscopy is performed on all patients receiving pneumothorax in whom there are: (1) visible adhesions, (2) patent cavities or (3) positive sputum. A total of 511 operations were performed on 431 patients. In 272 cases, completely selective collapse was obtained. In 77, there was selective collapse but the lung remained adherent to the upper mediastinum. In 44, satisfactory collapse was not obtained and, in 38, no adhesions could be cut. Adhesion section was completed in one stage in 364 cases, two stages in 57, three stages in 7 and four stages in one. Sputum was positive on admission in 343 cases, negative in 36; on discharge it was positive in 44, negative in 336. In most of the persistently positive cases, there were other explanations than inadequate sectioning of adhesions. A cavity was visible preoperatively in 372 cases, not visible in 15 and questionable in 6; postoperatively, a cavity was visible in 40, not visible in 342, and doubtful in 11. Postoperative temperature was recorded in 259 cases. In 172 cases, it did not exceed 99° F. It was over 99° F. for one to three days in 176 cases, for four to seven days in 46 cases and for more than seven days in 37 cases. Hemothorax occurred in 42 cases. Obliterative pleuritis developed in 5 cases; this resulted from hemothorax in one case, rapid reexpansion in 3 cases and pleural effusion in one case. No pleural effusion occurred in 207 cases; small transient effusions appeared in 87 cases and fluid sufficient to aspirate appeared in 106 cases. There were 26 empyemata, resulting from perforated tension cavities in 9 cases, fluid present prior to operation in one, tubercles on the pleura in one, hemothorax in one,

spontaneous rupture of adhesions in one, and no known cause in 9.—*Internal Pneumonolysis*, F. L. Wollaston, *Lancet*, September 20, 1947, 2: 424.—(A. G. Cohen)

**Unorthodox Pneumothorax.**—Determination of satisfactory collapse by X-ray evidence of diminution in the size of the lung suggests that only the mechanical effects of collapse are of value, whereas several other factors are operating within the chest. Retraction, relaxation and rest of the diseased areas may be of more practical consideration than the actual degree of collapse. Inflation of air into the pleural cavity may well act as a nonspecific type of shock, thereby inducing hyperemia of the pleural membranes which in turn affect the underlying parenchyma. Mechanical irritation of the pleurae by air as a foreign body, sudden increase in intrathoracic pressures or sudden changes in intrathoracic temperature, drying of the pleural surfaces and traumatic irritation of the parietal pleura by repeated needling may all be influential in producing changes in the physiological functioning of the vascular and lymphatic structures in the pleural-subpleural area. The resulting harmless pleurisy may influence the diseased lung quite independently of "collapse" proper; hyperemia, exudation and fibrin formation have a direct influence on the underlying tissue. Vascular and functional connections between pleura and lung are evidenced clinically by the usual association of nearly all primary lung lesions, for example, pneumonia, with pleural reactions. Conversely, pleural irritations and hyperemia are likely to lead to vascular reaction within the lung tissue. Such a relationship is seen clinically by cases of cavity closure after the development of a simple pleural effusion. Further illustration of this principle is demonstrated by the effectiveness of pneumoperitoneum following an exploratory laparotomy for investigation of abdominal tuberculous lesions. Six cases of pneumothorax are reported in this paper to show how favorable results were obtained in healing parenchymal disease in spite of inadequate collapse as measured by roentgeno-



logical evidence of degree of lung retraction. In most cases the treatments were abandoned after the development of an effusion in the presence of multiple adhesions. The probable biological and functional relationship between the pleura and underlying parenchyma should be recognized as a prime factor in the effectiveness of pneumothorax therapy in addition to the purely mechanical effects of lung retraction and immobilization.—*Unorthodox Artificial Pneumothorax*, E. G. Hoffstaedt & H. Miller, *Acta tuberc. Scandinav.*, 1947, 21: 169.—(P. Q. Edwards)

**Heart and Lungs in Thoracoplasty with Contralateral Pneumothorax.**—The cardio-respiratory effects of thoracoplasty with contralateral pneumothorax were studied in 10 patients: 7 men and 3 women (in one man on three different occasions and in another on two occasions). Maximum respiratory capacity for the whole group was found to be 48,000 cc. and minimum respiratory capacity 19,800 cc., while the respective figures for the women alone were 39,600 and 24,000 cc., the figures in both instances being much lower than in other groups studied. This shows that the combined procedure used in treatment decreased the available respiratory area more than any other collapse method. On the other hand, unilateral pneumothorax is the method affecting in the least degree respiratory capacity. Among 8 determinations in men signs of heart failure were seen in 6. In other words, as the respiratory area decreases, circulatory deficiency increases. The signs of cardiac trouble during exertion are again less common in unilateral pneumothorax and most frequent in thoracoplasty with contralateral pneumothorax. Bilateral pneumothorax and thoracoplasty behave indifferently, occupying an intermediate place between the other two procedures. Spirography with a simple metrolimeter shows readily whether aeration of the blood is adequate, obviating the use of gas analysis methods. The respiratory equivalent records most accurately whether a patient is hyperaerating or not. Hyperaeration is present when the respiratory equivalent

in an air environment exceeds the normal level (3:1) and drops to normal in an oxygen environment. An oxygen deficiency at rest is most unusual in collapse-treated patients. A psychogenous hyperaeration may lead to false interpretations and an exertion test is the best means to detect its presence. Determination of the maximum respiratory capacity permits determining what amount of overwork will cause an oxygen deficiency. An oxygen deficiency under exertion develops before the respiratory reserve is completely exhausted, but it seldom occurs while the reserve still exceeds 10,000 cc.—*Repercusión de la toracoplastia y neumotórax contralateral sobre la función cardio-respiratoria*, J. Sancho Carino, *Hispania méd.*, June, 1947, 4: 291.—(A. A. Moll)

**Types of Inexpansible Lung.**—The term "inexpansible lung," now so much in use in tuberculosis literature, should be better defined, and its confusion with chronic pneumothorax elucidated. A chronic pneumothorax is one which persists after the cessation of fillings. In order to call a lung "inexpansible," the organ must have collapsed as a result of an artificial pneumothorax. The added requirement of a dead pleural space is not essential. Actually, there are three types of inexpansible lung, namely, the chronic pneumothorax type with a gas or fluid-air-filled pleural space, the residual pleurisy or substitution effusion type with a fluid-filled pleural space, and the retractile hemithorax type without any intrapleural gas or air. Chronic pneumothorax is a sequel of a persistent pleural fistula. The other types are either the result of a rigid visceral pleura, of a sclerotic hardening of the parenchyma or less often of bronchial stenosis. For illustration purposes of the different types, 3 cases are reported all in women 18 to 34 years old. One was of chronic pyopneumothorax secondary to bronchopulmonary perforation, another of chronic partial hydrothorax following an effusion due to an inexpansible pulmonary lobe, and the third of hemithoracic retraction with large mediastinal pneumonocoeles as a

result of a completely inexpandible lung.—*Neumotórax crónico y pulmón inexpandible*, R. F. Vaccarezza & A. Soubrié, *An. cáted. de pat. y clín. tuberc.*, June, 1946, 8: 72.—(A. A. Moll)

**Blood Pressure in the Pulmonary Circulation in Men.**—In 5 patients in a hopeless condition—4 of them with meningeal tuberculosis—the pressure in the pulmonary artery was determined through a puncture in the thoracic wall. A Hamilton manometer was used to register changes in pressure. The median values obtained, varying from 14.5 to 27.8 mm. and averaging 19.2 mm., were compared to those revealed simultaneously by the femoral artery, which varied from 114.9 to 154.7 mm. The ratio between the two varied from 1:4.1 to 1:10.2 and averaged 1:7.2. This agrees with the results in animals. The case with the highest pulmonary and lowest general blood pressure had an artificial pneumothorax, and this may have influenced the results. The effect of the respiratory movements was apparent in both circulations, although not necessarily parallel.—*Determinación de la presión arterial pulmonar en el hombre*, R. F. Vaccarezza, A. Lanari & V. A. J. Alberti, *An. Cáted. de pat. y clín. tuberc.*, June, 1946, 8: 29.—(A. A. Moll)

**Return Venous Flow and Pulmonary Blood Pressure.**—Experiments in cats with uncut chests, with closed (fenestrated) chests but with the heart exposed, and with chests cut open, failed to show any corresponding increase or decrease in the blood pressure in either the pulmonary or the systemic circulation which would parallel changes in size in the return venous flow.—*Influencia del flujo venoso sobre la presión arterial pulmonar*, V. A. J. Alberti, *An. Cáted. de pat. y clín. tuberc.*, June, 1946, 8: 89.—(A. A. Moll)

**Pulmonary Circulation and Systemic Blood Pressure.**—Experiments in cats showed that clamping of one of the branches of the pulmonary artery is followed by a slight transitory drop in the general blood pressure. When

the main trunk is blocked the drop in pressure becomes progressive. In both instances a most marked pulmonary hypertension develops. In the one case in which a persistent hypotension in the systemic circulation occurred, this was attributed to the presence of heart failure, as confirmed by a similar drop in the pulmonary pressure.—*Variaciones de la presión arterial general consecutivas a la segregación parcial o total de la circulación pulmonar*, V. A. J. Alberti, *An. Cáted. de pat. y clín. tuberc.*, June, 1946, 8: 101.—(A. A. Moll)

**Hilar Anatomy.**—In order to study the surgical anatomy of the hilar area, 50 lungs were dissected, the results being presented in a series of 17 illustrations. Jackson and Huber's classification, dividing the right lung into 10 and the left lung into 8 bronchial segments, has been adopted. The surgeon must keep in mind the crossing formed by the bronchial tubes leading to the middle and upper lobes and the middle basal segment with the tube for the other basal segments. In opposition to Boyden's views, the tube for the middle basal segment was found to start at the same level as the tubes for the upper and the middle lobes. In the right upper lobe and also in the middle lobe the presence of two collateral arteries is most common. A single collateral artery and three collateral arteries were found only once each. In the basal lobe, a single artery is the usual thing, but finding two collateral arteries is not uncommon. Striking venous abnormalities were seen in the right side. In one case, a vein from the upper lobe emptied into the upper cava, and in 2 other cases all the blood from the middle lobe drained through a single vein into the lower pulmonary vein. In another case, a vein from the left upper lobe emptied into the upper pulmonary vein. With but one exception, the lingual veins were tributaries to the upper pulmonary vein. The significance of the relations between the points of origin of the different arteries is emphasized. The presence of old healed processes and imbedded calcified nodes complicates the surgeon's task.

The significance of this paper, first of a series, is clearly brought out in its original illustrations.—*Contribución al estudio de la anatomía quirúrgica del hilio pulmonar*, L. Gercz Maza, J. Rodríguez Arroyo & I. Purpón, *Rev. mex. de tuberc.*, July, 1947, 8: 215.—(A. A. Moll)

#### Streptomycin in Experimental Tuberculosis.

—Experiments on 161 mice, using one or two milligrams of streptomycin daily, confirm the efficacy of this treatment for experimental tuberculosis. It does not entirely destroy the tubercle bacilli but stops their multiplication. This bacteriostatic effect aids the body cells in destroying or encapsulating the tubercle bacilli but there is no true sterilization. In spite of the prolonged survival of the animal, the organisms remain living and virulent and cessation of the treatment may be followed by reactivation of the disease. There is a striking similarity between test tube and animal experiments and the results of clinical observation.—*Etude expérimentale de l'activité thérapeutique de la Streptomycine dans la tuberculose*, C. Levaditi & A. V. Vaisman, *Institute Alfred Fournier Paris, Presse méd.* September 20, 1947, 54: 611.—(E. Bogen)

**Streptomycin Therapy.**—Seventeen patients, 12 adults and 5 children, with meningeal, miliary or other forms of generalized hematogenous tuberculosis were treated with streptomycin. Highly purified streptomycin sulfate was administered for 120 days. Adults received a daily dose of 3 g. intramuscularly in six or eight divided doses; children received 20,000 mcg. per kilogram of body weight. Patients with meningitis received additional intrathecal streptomycin in doses ranging from 0.05 g. to 0.375 g. at intervals of twenty-four to seventy-two hours for periods of sixty to ninety days. The larger intrathecal doses were not well tolerated and the 0.1 g. dose was not exceeded during most of the investigation. Cultures for tubercle bacilli were made at two-week intervals during and following therapy. All tubercle bacilli were tested for drug sensitivity using the Dubos medium. There were 9 patients with bacteriologically proved

meningitis. In 7, the meningitis was a complication of acute miliary tuberculosis; all 7 have died. The remaining 2 did not have miliary disease and have been in remission for five months following treatment. In the majority of patients who died, the meningitis ran a subacute or asymptomatic course and the clinical picture was dominated by the miliary tuberculosis. One infant died of internal hydrocephalus; postmortem examination revealed almost complete healing of the meningeal process. The 2 patients in remission show no clinical signs of neurological disease and the only spinal fluid abnormality is an elevated protein. Meningitis did not appear as a complication of miliary tuberculosis until after thirty-five to ninety-six days of streptomycin therapy. The meningitis often appeared at a time when the miliary disease appeared to be receding. The addition of intrathecal streptomycin resulted in some improvement but these patients went on to death or relapse in from twenty to 124 days after the first evidence of meningitis. After intrathecal therapy was started, the principal changes in the spinal fluid were disappearance of bacilli and increase of sugar. Irrespective of eventual outcome, the spinal fluid cell count and sugar remained elevated as long as treatment was continued. When treatment was stopped, the cell count fell rapidly but the protein remained elevated for long periods; these changes may be due to irritating effects of the drug. After a period of initial improvement in 13 patients with acute miliary tuberculosis, the clinical course followed one of four patterns: (1) Attainment of complete remission sustained for at least six months without therapy. This occurred in 2 patients. Much of the X-ray clearing occurred following completion of therapy. (2) Continued improvement with transformation of acute infection into chronic disease: one patient. (3) Remission of miliary infection with death from meningitis; one patient. Complete remission of the miliary disease was confirmed by post-mortem study. (4) Partial or complete remission followed by fatal relapse despite uninterrupted treatment. This occurred in 5

patients and was the most frequent pattern. Relapse appeared as early as twenty days following institution of therapy and as late as three and one-half months after cessation of treatment. Tubercle bacilli isolated from 4 of these 5 patients at onset of relapse were highly drug-fast *in vitro*. One patient with tuberculous pericardial effusion and lymphadenitis and one with disseminated bone disease showed marked clinical improvement. There was rapid healing of draining sinuses in the latter case. No X-ray changes in the bone lesions have been noted during an eleven-month period. The patient with pericarditis is well and ambulatory eleven months after completion of treatment. Tubercle bacilli isolated before treatment in 15 of the 17 patients showed marked drug sensitivity, and, in general, were inhibited by less than 2 mcg. per cc. The shortest period required for appearance of resistance was thirty-four days. In 2 patients, before institution of intrathecal treatment, organisms isolated from spinal fluid were sensitive even though bacilli from the accompanying systemic infection had already been rendered resistant (organisms not inhibited by concentrations of 500 mcg. per cc.) by previous parenteral treatment. There was a definite correlation between failure of therapeutic response and appearance of *in vitro* resistance. Resistant organisms were never isolated from the 7 patients who attained satisfactory remissions. Six of the 7 fatal cases of acute miliary tuberculosis have been examined postmortem. Varying degrees of healing were observed. Complete healing of miliary lesions was seen in the infant who died of internal hydrocephalus. One patient presented the picture of partially healed tubercles which had broken down to form recent active disease. Tuberculin testing at monthly intervals during and after treatment revealed no significant changes. Observations on development of drug-fastness suggest that it may be best to limit streptomycin treatment to only six or eight weeks in order to decrease the risk of relapse with resistant organisms. The low incidence of successful treatment in meningitis may be due, in part, to the fact

that the natural mechanisms of defense are less efficient in the central nervous system than in the lung.—*Streptomycin in the Treatment of Tuberculosis in Humans: I. Meningitis and Generalized Hematogenous Tuberculosis*, W. McDermott, C. Muschenheim, Susan J. Hadley P. A. Bunn & Rosemary V. Gorman, *Ann. Int. Med.*, November, 1947, 27: 769.—(H. R. Nayer)

**Streptomycin Therapy in Greece.**—Seventy-eight patients with tuberculosis treated at the Sismanoglion Tuberculosis Institute in Athens before May, 1947 showed striking improvement in spite of the small amount of streptomycin available. The majority received only one ounce or less total dose and none had had more than a few months of treatment. Although the figures in the tables in Greek and in English do not quite balance and the data are premature and far from sufficiently critically studied, they support similar findings elsewhere.—*Streptomycin in the Treatment of Tuberculosis*, S. Papacmanuel, Director General & Director of the First Pathologic Clinic, Sismanoglion Tuberculosis Institute, Athens, May, 1947, 80 pages in Greek, 22 pairs of X-ray illustrations, 28 references in bibliography and complete English translation, totaling 200 pages, paper bound, Athens, 1947, private publication.—(E. Bogen)

**Streptomycin in Tracheobronchial Tuberculosis.**—The results obtained with streptomycin in 5 cases of tracheobronchial tuberculosis encourage the belief that the long sought specific treatment for this condition is at last in sight. Systemic treatment should, of course, aim primarily at the lesion in the lung while topical care should be based on the circumstances of the individual case. Up to now, cauterization with silver nitrate has been used with fair results in the way of improvement, but occasionally tenderness and even progression of lesions occurred. The series studied includes 186 patients in a 4.5-year period. Among them, 141 had pulmonary tuberculosis and 67 (46.2 per cent) tracheobronchial lesions. Prevalence in pulmonary cases averaged 16

per cent. Best diagnostic guides are clinical signs and symptoms and X-ray findings, the former being more reliable. Bronchoscopy should be undertaken only when symptoms suggest the possibility of complications developing as a result of the treatment advised. Thoracoplasty, if feasible, is the treatment of choice when tracheobronchial involvement is associated with lesions in the upper lobe. When successful, tracheobronchial lesions heal spontaneously. Aspiration of residual cavities following pneumothorax and atelectasis may prove useful.—*Tráqueobronquite tuberculosa*, E. Etzel, *Clin. fisiol.*, (Rio de Janeiro), April-June, 1947, 2: 167.—(A. A. Moll)

**Antibiotics.**—The history of antibiotic treatment of tuberculosis is reviewed from the first application of bacteriotherapy by Catani in 1885 to the most recent investigations. Antibiotics are produced by various members of all major groups of microorganisms, namely, fungi, bacteria and actinomyces. Among the fungi *Aspergillus fumigatus* received particular attention (fumigacin). Antituberculosis properties of the spore-forming aerobic bacteria were also given special consideration; subtilin, eumycin and bacillin are the best known preparations. Other antibiotics were obtained from some non-spore-forming bacteria (pyolipic acid) and from certain streptococci. The actinomyces comprise a number of organisms which produce antibiotics active against tubercle bacilli: actinomycin, litmocidin, nocardin, streptothricin and streptomycin. Some higher plants produce substances with tuberculostatic and tuberculocidal properties (phytoncides). Indications for and results of streptomycin treatment are discussed in detail.—*Antibiotics and Tuberculosis: A Microbiologic Approach*, S. A. Waksman, J. A. M. A., October 25, 1947, 135: 478.—(H. Abeles)

**Tuberculous Meningitis.**—A patient with miliary tuberculosis and proved tuberculous meningitis was treated by intrathecal and intramuscular administration of streptomycin.

The patient recovered completely and remained well during a follow-up period of nine months.—*Tuberculous Meningitis and Miliary Tuberculosis Arrested with Streptomycin*, E. Applebaum & C. Halkin, J. A. M. A., September 20, 1947, 135: 153.—(H. Abeles)

**Tuberculous Meningitis.**—A patient with a pleural effusion and minimal pulmonary tuberculosis developed tuberculous meningitis while under treatment by bed-rest. Early administration of streptomycin resulted in recovery from the meningitis.—*Streptomycin in Tuberculous Meningitis*, C. P. Mehas & W. E. Truax, J. A. M. A., September 20, 1947, 135: 155.—(H. Abeles)

**Tuberculous Rheumatism.**—A boy aged 16 developed a sore throat. Four days later pleuritic pain appeared. Later there was X-ray evidence of infiltration of the lung and enlargement of the mediastinal nodes. Still later there was a febrile episode with pericarditis, myocarditis and joint pains. This eventually subsided. The tonsils were then removed; histological examination revealed caseous tuberculosis. Three weeks later the patient developed a pleural effusion. The sequence of events leads the author to believe that the joint symptoms were a manifestation of tuberculosis.—*Tuberculous Rheumatism*, R. J. T. Woodland, *Lancet*, October 11, 1947, 2: 540.—(A. G. Cohen)

**Gland Biopsies in Joint Disease.**—Valls, of Buenos Aires, (1933) first published the results of lymph gland biopsy as an aid in the diagnosis of tuberculous bone and joint disease. This paper reports the results of 100 gland biopsies carried out to assist in the diagnosis of arthritis in various joints. The iliac gland was the one used routinely for hip and upper femoral disease, the inguinal gland for infections of the knee, ankle, and foot, and the axillary glands for joints of the upper limb. There were 33 (56 per cent) positive results in 59 cases of tuberculous infection. A positive biopsy does not necessarily mean that the joint is tuberculous, because it may be an old

burned-out process not related to the localized joint infection. Positive results seem to be more likely if the biopsy is done early in the disease (71 per cent). An early positive biopsy gives strong support to a tuberculous infection and may appear before X-ray changes. Gland biopsy should be added to other clinical findings, including X-ray and sedimentation rate, to obtain an accurate diagnosis of chronic bone and joint disease.—*Lymph Gland Biopsies for Suspected Bone and Joint Tuberculosis: An Analysis of 100 Consecutive Cases*, G. P. Arden & J. C. Scott, *Brit. M. J.*, July 19, 1947, 4515: 87.—(R. W. Clarke)

**Adrenal Function in Tuberculosis.**—The Robinson, Power and Kepler test for adrenal insufficiency was performed in 32 cases of pulmonary tuberculosis. These patients did not have clinical Addison's disease. In 13 of these the test was positive, indicating some degree of adrenal cortical insufficiency. The test was found to be positive more frequently in patients in poor general condition. The individuals with positive tests were treated with a synthetic cortical hormone (Corticon or Percorten) for varying periods of time, resulting in a reversal of the Robinson, Power and Kepler test to normal in all cases except one.—*La prueba de Robinson, Power y Kepler en enfermos con tuberculosis pulmonar*, J. Casas Carnicero & E. Aguiar Soto, *Rev. españ. de tuberc.*, July, 1947, 16: 523.—(F. Perez-Pina)

**Fluorescence Microscopy for Detecting Tubercle Bacilli.**—By using a two-thirds inch objective in fluorescence microscopy a smear may be traversed at a greater speed than possible when using an oil immersion objective in normal microscopy, since the brightly fluorescing tubercle bacilli readily attract the eye. Therefore, by using this method one should expect an increase in the number of positives obtained. This theory was put to test in a hospital of 210 beds. Prior to this investigation, a study of 500 direct smears of sputum yielded 45 per cent positives. In this investigation, 500 consecutive routine sputum

specimens were studied by both methods. All smears were first examined by the fluorescence method; they were then restained by the Ziehl-Neelsen method and reexamined on the following day without knowledge of the previous findings. The time elapsing from the first focusing to the first detection of bacilli was noted. Negative reports were rendered only when the same smear was examined by each method for eight minutes. Cultures were made in cases where one or both methods gave either negative or doubtful results. As a result of these studies, it was found that the modified Ziehl-Neelsen technique yielded 1.4 per cent more positives with an expenditure of less time than that required by the fluorescence technique. The modified Ziehl-Neelsen method required an average of six seconds less time per smear. In the case of the Ziehl-Neelsen technique, more than twice the number of doubtful positive results were confirmed by culture than was true for the fluorescence technique. It is concluded that the fluorescence technique does not offer advantages over the Ziehl-Neelsen procedure. The value of cultures in cases of negative or doubtful positive smears is established.—*Detection of Mycobacterium Tuberculosis by Means of Fluorescence Microscopy*, G. D. A. Briggs & M. H. Jennison, *Tubercle*, September, 1947, 28: 189.—(A. G. Cohen)

**Laryngeal Swab Cultures.**—Laryngeal swabs for serial culture specimens are being used quite extensively in situations where obtaining gastric specimens is not feasible or practicable. The possible shortcoming of this method—a lesser yield of positives—is overcome by the more frequent taking of specimens for examination. The technique employed successfully involves placing a sterile swab carefully in the laryngeal area, behind the epiglottis, while the patient is asked to cough. Droplets of coughed sputum are thus collected on the swab, which is then replaced in a sterile test tube for neutralization. Fluid medium is added to the swab, and from this two tubes of solid egg medium are

inoculated. The swab is not discarded at this time but rather immersed in another tube with fluid medium—the “deep swab culture”—in order to utilize all available cough droplets containing bacilli. Positive results from this method vary from 13.5 to 28.8 per cent among patients whose sputum is negative on microscopic examination.—*Deep Swab Culture: A New Method for Cultural Demonstration of Tubercle Bacilli*, L. Sula, *Acta tuberc. Scandinav.*, 1947, 21: 160.—(P. Q. Edwards)

**Depth Cultures for Tubercle Bacilli.**—Except in rare cases, it appears that until recently tubercle bacilli did not grow, or grew poorly, in the depth of liquid media when a small number of bacilli were inoculated. Besredka's medium enables deep growth of young cultures in very small amounts:  $10^{-5}$ ,  $10^{-6}$  and  $10^{-7}$  mg. The duration of the latent phase of the culture which extends from three days to one month or more varies with the type of bacilli, the particular batch, and the richness of the inoculum.—*Sur La végétation du bacille de Koch en profondeur*, A. Boquet & A. Andrejew, *Ann. Inst. Pasteur, Septemher*, 1947, 73: 928.—(P. Q. Edwards)

**Streptomycin Titration.**—The titration of streptomycin against several organisms produced results with wide variations. The lowest readings were obtained in broth (with one exception), and invariably the highest readings were found in serum-water medium. The results in human blood are usually considered higher than in broth. The salt content of the medium is important, and to some extent saline solutions inhibit streptomycin. It was found that with some test organisms a higher concentration of streptomycin was required to inhibit growth in an anaerobic environment. In using capillary tubes and test tubes, it was noted that when both were open the results were identical, that when the capillaries were sealed in flame, more streptomycin was required to inhibit growth, and that still more was needed when they were incubated vertically. This may

be due in part to the diminished access to air in the closed tubes. These results were obtained with *B. coli*, Friedländer's bacillus and staphylococcus, but when streptococcus was used as the test organism, the end point was the same whether the capillaries were open or closed and whether they were incubated horizontally or vertically. When testing normal sera for streptomycin, the sera should be inactivated before use. Inactivation of by heat (half an hour at 56° C.) did not destroy the streptomycin. The method for titrating streptomycin in serum is given in detail.—*Some Problems in the Titration of Streptomycin*, J. R. May, A. E. Voureka & A. Fleming, *Brit. M. J.*, May 10, 1947, 4505: 3.—(R. W. Clarke)

**Purified Tuberculin.**—Shortly after the appearance of PPD, investigations were begun in Denmark to find an adequate and practically serviceable method for the production of purified tuberculin. These investigations resulted in the procedure published in 1938 by K. A. Jensen, Bindselev, Møller, Hansen and Lind. During the performance of these experimental investigations it was realized that the very method for the preparation of purified tuberculin as well as the properties of the purified tuberculin were associated with many problems that might be investigated. These studies were begun in 1940 and the outcome is the present paper. Detailed description is given of the technique employed in the production of purified protein as well as pertinent historical background material.—*Purified Tuberculin, Its Preparation and Properties*, P. Lind, *Acta tuberc. Scandinav.*, 1947, 21: 111.—(P. Q. Edwards)

**Tuberculin and Tubercle Bacillus Allergy.**—Simultaneous comparisons of tuberculin reactions and cutaneous BCG reactions in 124 allergic persons in various stages of a tuberculous infection showed a high degree of parallelism. The BCG tests were made by pricking the skin two or three times, using a vaccine containing 20 mg. BCG per cc. Tuberculin tests were the usual Mantoux test, read in

forty-eight hours. In general, the size of the pustules and the duration of the reaction ran a course parallel to that of the size of the infiltrations caused by the tuberculin. Tuberculin allergy, however, showed a wider range of fluctuation than BCG allergy. Experimental studies with guinea pigs revealed a comparatively insignificant reduction in the size of BCG reactions after tuberculin desensitization of the animals. Combined desensitization with tuberculin and BCG reduced the reaction to cutaneous BCG tests more effectively than desensitization with tuberculin alone or BCG alone. This may be caused by injection with BCG of certain other substances having the same action as tuberculin, the differences observed in the reactions being explained as the result of increased tuberculin desensitization. If this were so, one would expect to find a similar difference in tuberculin reactions in the corresponding groups. This was not the case. There would seem to be no reason for assuming that the animals given BCG injections as a supplement to tuberculin were essentially better tuberculin-desensitized than the animals treated with tuberculin alone. Experimental results seem to fit in best with the assumption that the tubercle bacillus contains other allergens than the antigens in ordinary tuberculin and that it is possible to a certain extent to desensitize the organism in relation to these other allergens.—*The Connection between Tuberculin Allergy and Tubercle Bacillus Allergy*, O. K. Thomasen, *Acta tuberc. Scandinav*, 1947, 21: 87.—(P. Q. Edwards)

**Tubercle Bacilli and Isoallergic Encephalomyelitis.**—This work extends the recent observations made by Morgan, and Kabat, Wolf, and Bezer, that encephalomyelitis may be produced in rhesus monkeys by a few injections of suspensions of homologous nervous tissue combined with killed tubercle bacilli and water-in-oil emulsion. In the present investigation the authors employed guinea pigs treated with either guinea pig or rabbit brain combined with water-in-oil emulsion and human tubercle bacilli or

*M. butyricum*. A single subcutaneous injection induced paraplegia three or four weeks later in most animals. The brain tissues of both species of animal were effective and either acid-fast bacillus could be used. Animals which received the rabbit brain also developed delayed cutaneous sensitivity to this material; those which received guinea pig brain did not develop such responsiveness. Other tissues employed in the same combination did not cause neurologic symptoms nor lesions. Histologic study revealed vascular lesions in the brain, cord and some of the anterior roots of the cord. These consisted of thrombosis, perivascular infiltration, occasional microscopic hemorrhages, and the accumulation of inflammatory cells in the parenchyma. The authors believe that these reactions are probably allergic in nature, since the effect could not be transferred passively and because of the occurrence of cutaneous and systemic reactions to nervous tissue antigen.—*Isoallergic Encephalomyelitis and Radiculitis in Guinea Pigs after One Injection of Brain and Mycobacteria in Water-in-Oil Emulsion*, J. Freund, E. R. Stern & T. M. Pisani, *J. Immunol.*, October, 1947, 57: 179.—(S. Raffel)

**Radiologic Aspects of the Lung in Circulatory Insufficiency.**—This subject has been reviewed by a number of French writers to whom the author refers. The hilar shadows are due essentially to the pulmonary arteries. Their exact topography has been determined precisely by postmortem opacification of the arteries, and in the living by angio-pneumography. The pulmonary veins, on account of their more reduced calibre and their location, normally have no part in the radiologic picture of the hilum. The framework of the parenchyma is indicated by multiple branching shadows of arteries and arterioles, closely connected with the bronchi and bronchioles. Stasis of the blood can be measured by determination of the circulation time (arm-tongue tests) and this permits one to distinguish between dyspneas of cardiac and those of respiratory origin. The presence of râles is



not necessarily a sign of stasis. It simply indicates the presence of fluid in the bronchioles. An important element in radiologic diagnosis is the heart silhouette, which is always altered. General clinical examination is always necessary and may be very helpful in interpretation of shadows. Dyspnea is always marked. The X-ray is only one element in the diagnosis. Radiologic anomalies are of three classes: vascular, parenchymatous and pleural. Vascular anomalies include hilar and trabecular changes. The hilar structures, especially on the right, are more evident, but their borders are somewhat less well defined and faint. Their central areas are denser than under normal conditions and vary with the degree of cardiac insufficiency present. The pulmonary veins filled with blood may become visible. The first stage of change in the parenchymal area consists in the appearance of rounded nodules due to the crossing of shadows of over-filled arterioles or alveolar exudates, which may vary in size in the two lung fields. These may combine to form areas of irregular size rather easily mistaken for early tuberculosis, especially as the patient may also have slight hemoptysis. In certain cases there is enlargement of the azygos vein which may be as large as a thumb. Sometimes the crook of the azygos vein forms an obtuse angle with the right bronchus in which a shadow like an inverted comma appears; this indicates congestion. The azygos vein itself becomes enlarged when there is increased venous pressure. The presence of fluid in an interlobar fissure may make definite opaque lines or bands in certain cases. In other cases the shadows are not as well defined and can only be brought out in special positions. Sometimes rounded or racquet-shaped shadows are produced. Transudates into the large intrapleural cavities produce familiar radiologic pictures, too well known for special comment and not likely to cause diagnostic difficulties.—*Aspects radiologiques du poumon au cours de l'insuffisance circulatoire*, H. Durieu, *Rev. belge de tuberc.*, 1947, No. 2, 182.—(A. T. Laird)

**Cavernoscopy and Cavernography.**—Cavernograms become essential for exploratory purposes in order to define the surgical problem in the presence of tuberculous cavities. They will also help in judging the advisability of trying a preliminary aspiration according to Monaldi's method. A typical case is described to show that, in a cavitary process where collapse does not seem feasible with the routine methods, the walls may not be as rigid as believed and retraction is still possible. Fluoroscopy and roentgenography may suggest a larger amount of lost parenchymal tissue than is actually the case, and there may be around the cavity compressed pulmonary tissue which may reexpand under favorable conditions and promote the healing of the cavity. Cavernoscopy is a most valuable and harmless supplementary exploratory aid. It should be used especially in cirrhotic cavities to appraise the degree of collapse to be obtained with surgical measures and the type and shape of the outlet of the draining bronchial tube. Cavernoscopy was tried in 10 cases with Maurer's thoracoscope, either as a preliminary to endocavitary aspiration or as an independent means of exploration.—*Estudio de la caverna tuberculosa por el cavernograma y la cavernoscopia*, J. A. Verna, S. A. Sarmiento & C. Ludueña Funes, *Arch. de Secretaria de Salud Pùb. Nac.*, March, 1947, 1: 5.—(A. A. Moll)

**Pneumonia in Egyptian Children.**—Three hundred cases of pneumonia in children of poor families were treated in the two years before April, 1947. The incidence was highest in children under 2 years of age, the fatality rate was highest in those less than a year of age, and the greatest number of cases (78 per cent) occurred between December and May. Lobar pneumonia was diagnosed in 206 cases: 107 were given chemotherapy (chiefly sulfadiazine), and had a fatality rate of 5.6 per cent, and a complication rate of 9.4 per cent; 99 were given penicillin, with a fatality rate of 1.1 per cent, and complications in 8 per cent. Crises within twenty-

four hours occurred twice as often with penicillin. Bronchopneumonia was diagnosed in 94 cases: 40 received chemotherapy, with a 25 per cent fatality and a 20 per cent complication rate; 19 received penicillin, with a 21.2 per cent fatality, and a 20.8 per cent complication rate; 35 received both drugs, with an 8.6 fatality and 5.7 per cent complication rate. Penicillin-in-oil was given in a single massive dose (25,000 to 30,000 units per Kg. body weight) to 24 children with lobar pneumonia: there were no deaths, and 91.6 per cent recovered completely, with crises in the first day. Because of the simplicity and good results of this method, it may become the treatment of choice for children.—*Pneumonia in Children*, A. S. A. Abbasy, *Arch. Pediat.*, August, 1947, 64: 403.—(W. H. Oatway, Jr.)

**Pneumonia Caused by Proteus.**—A 63-year-old woman was hospitalized with the complaints of chills, vomiting, nausea and diarrhea. Urine and feces cultures were positive for *Proteus mirabilis*. On the eleventh hospital day the patient developed a high fever and a right basal pneumonia. Blood and sputum cultures were positive for *Proteus mirabilis*. The patient was treated with penicillin and streptomycin but neither of them exerted a direct effect on the primary infection. The patient was discharged from the hospital after sixty days.—*Pneumonia Due to Proteus Mirabilis Treated with Penicillin and Streptomycin*, L. D. Snorf, L. Shepanek, E. E. Foltz & H. Harding, J. A. M. A., September 27, 1947, 135: 222.—(H. Ables)

**Rheumatic Pneumonitis.**—A 25-year-old white woman with mitral stenosis with repeated bouts of congestive failure was seen. The patient had several febrile episodes during which leucocytosis and neutrophilia were observed. Chest roentgenograms showed a confluent pneumonic consolidation of the base of the right lung. The diagnosis of rheumatic pneumonitis was considered. The findings

at autopsy were: mitral stenosis, verrucous endocarditis, myocarditis, pneumonopathy with diffuse fibrosis and partly healed arteritis, chronic passive hyperemia, acute parenchymatous degeneration of liver and kidneys. The pulmonary lesions were the same as those found by others in rheumatic pneumonitis.—*Rheumatic Pneumonitis: A Case of widespread (Proliferative) Type with Acute (Exudative) Foci*, E. E. Muirhead & A. E. Haley, *Arch. Int. Med.*, September, 1947, 80: 328.—(G. C. Leiner)

**Pleurodynia.**—From July to November, 1947, a large number of cases of "pleurodynia" were seen in the Boston area. The disease generally appears in the late summer or early fall. It affects mostly young people. It is characterized by a sudden onset of pain in the abdominal region, generally along the line of attachment to the diaphragm. The pain is aggravated by motion and breathing. The temperature may go as high as 104° F. but often falls within twelve hours. There may be one or two recrudescences of pain and fever during the following ten to fourteen days. Examination reveals splitting of the chest or upper abdomen. Thoracic tenderness and a friction rub may or may not be present. X-rays are normal. The total white blood count is normal but there may be an eosinophilia during convalescence. Complications are rare and consist of orchitis, pericarditis and jaundice.—*Pleurodynia*, J. J. Finn, Jr., *New England J. Med.*, October 23, 1947, 237: 621.—(A. G. Cohen)

**Coccidioidomycosis.**—Four cases are presented, all of men who had performed military service in endemic areas several years previously. All had minimal pulmonary lesions in the subsiding phase. One patient had an active granulomatous lesion of the lip.—*Coccidioidomycosis in New England*, E. R. H. Kurz & N. W. Loud, *New England J. Med.*, October 23, 1947, 237: 610.—(Q. G. Cohen)

**Coccidioidomycosis.**—The spherules of *C. immitis* remain viable under certain conditions

and do not produce hyphae and chlamydo-spores in exudates from human sources for at least 110 days. By instilling spherule-containing sputum or exudates from human or animal sources into the bronchi of guinea pigs and propelling them by air pressure into the finer ramifications of the bronchioles and alveoli, it is possible to produce coccidioidomycosis in 100 per cent of the animals. The lesions are localized for the most part in the upper portions of the lungs, are single or multiple, have a lymph node component and are not generalized, thus simulating the human infection. These experiments show that spherules (or sporangia) can be infective through the respiratory route from man to animal and from animal to animal. It is concluded that active primary or progressive coccidioidomycosis in human beings should be considered contagious until proved otherwise. (Authors' summary.)—*Contagiousness of Coccidioidomycosis: An Experimental Study*, S. R. Rosenthal & J. B. Routien, *Arch. Int. Med.*, September, 1947, 80: 343.—(G. C. Leiner)

**Pulmonary Hydatid Disease.**—A case of hydatid cysts of the lung, requiring three operations in a two-year period, and taken out of a large series, is described at length to drive home certain telling points in this branch of thoracic surgery. This is important in a country such as Uruguay where the condition is so prevalent. Pulmonary echinococcosis causes no symptoms in its early stages. When signs and symptoms develop following spread, it is already too late for effective treatment. The remedy is to conduct annual fluoroscopic mass surveys in all infected areas. The time to operate is before complicating lesions develop, as these can be cured only through extensive pulmonary resections. As the repeated dangerous hemoptyses are due to openings into the bronchial system, the only definite hope of cure lies in a lobectomy in the sector involved to remove all possibility of further spread from the infected lobe. Sec-

ondary cysts develop at the rate of 3 to 3.5 cm. a year. The old division of cysts into central and peripheral must be discarded with its implied suggestion that different methods are required to handle them. In order to minimize chances of contamination, cysts are no longer drained before removal. The pulmonary parenchyma is now cut open above the projecting cyst, bleeding is controlled by pressing together the cut ends between the forefinger and thumb, and as the gas pressure is increased by the anesthetist, the entire cyst is pushed out. The opening may be sewn together immediately as there is no inside contamination. Through visual examination and palpation it is easy to locate all cysts present, once the pulmonary parenchyma is completely collapsed. Total lobectomy may be considered in the presence of many scattered cysts in the same lobe. When they are small, cyst removal seems preferable. In the case described, four cysts were taken out of the middle lobe in preference to lobectomy, and the lobe later became adequately functional. This course proved most wise, as an irreversible lesion in the left lower lobe will eventually compel its removal.—*Equinococcosis pulmonar: Su tratamiento quirúrgico*, J. Soto Blanco, *Hoja fisiol.*, June, 1947, 7: 101.—(A. A. Moll)

**Chronic Pneumothorax as Sequel to Pleural Fistula.**—In 8 cases of chronic pneumothorax, the coexistence of a bronchopleural fistula was demonstrated through examination of the pleural gas contents. In any case of persistent pneumothorax with no decrease of the gas contents after discontinuing fillings for three months, a diagnosis of pleural fistula is justified. Any persistence of pleural distension in such cases calls for a study of the gas contents to confirm or disprove the diagnosis.—*Estudio de los gases pleurales en el neumotórax crónico*, P. F. Vaccarezza, A. Soubricé & F. H. Labourt, *An. cáted. de pat. y clín. tuberc.*, June, 1946, 8: 59.—(A. A. Moll)

# DELAYED CHEMICAL PNEUMONITIS IN WORKERS EXPOSED TO BERYLLIUM COMPOUNDS<sup>1</sup>

HARRIET L. HARDY<sup>2</sup>

During the past five years, with the increased industrial use of beryllium compounds for both military and civilian purposes, a remarkable clinical syndrome has become evident. The present report consists of an analysis of the principal findings in 36 patients who presented the characteristic picture of this syndrome.

Beryllium compounds are derived from beryl ore which occurs in India, Brazil, Russia and in small amounts in the U. S. A. Beryllium combined with copper or aluminum results in an alloy of unusually light and fatigue-resistant character. This has been the chief industrial use for beryllium. In 1938, the use of beryllium as a constituent of fluorescent powders began. The Smyth report reveals that the Manhattan Project used beryllium.

Scrutiny of the literature shows that industrial illness was reported from Russia (3, 4), Italy (2) and Germany (1, 5, 6, 7) between 1933 and 1942 in operations where workers were exposed to beryllium compounds. The reports in this country of similar occurrence appeared first in 1943 (8) and have since been published annually. In Europe, as in the U. S. A., pulmonary disease has been most prominently reported.

Published animal experimentation does not at present yield a clear-cut picture of predictable toxic effects. There are reports of lung pathology and bone pathology produced by the administration of beryllium compounds to various laboratory animals. The U. S. Public Health Service (9), in an exhaustive study of the toxicology of beryllium published in 1943, could not establish that the metal beryllium is of itself harmful.

## NATURE AND COMPOSITION OF MATERIAL

The 36 clinical records which form the basis for the present report were made available through the courtesy of the physicians caring for these patients. The records cover the cases of 12 men and 24 women engaged in all phases of the manufacture of fluorescent lamps. The material used to coat these tubes is a mixture of zinc, manganese, and beryllium silicate, which has the property of fluorescing when exposed to ultraviolet light. Interest became fixed on the beryllium component of the fluorescent powder mixture, since there is considerable knowledge of industrial diseases associated with zinc, manganese and silica exposure, and the illness here reported corresponded with none of these. The first 2 cases, cared for by different physicians and hospitals, appeared in 1941; but in each

<sup>1</sup> Presented before the Medical Section, as part of the symposium on *Pulmonary Diseases in Industry*, at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 19, 1947.

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successive year more cases have gradually become known, as may be seen in table 1. There is no known environmental reason for the peaks of incidence in 1943 and 1946. Due to war needs, the workers came from a wide area, and the knowledge that this group of cases belonged together because of the common denominator of exposure to beryllium compounds was not evident until two years after the appearance of the first case.

TABLE 1  
*Occurrence of cases*

YEAR	NUMBER OF CASES
1941	2
1942	2
1943	10
1944	3
1945	7
1946	12
Total . . . . .	36

#### CLINICAL SYNDROME

As the cases have been studied during the past five years, a unique clinical syndrome has been delineated.

*Onset:* The histories reveal that, in 20 out of 32 cases, there has been a delay in onset of symptoms of from one month to four years from the last date of ap-

TABLE 2  
*Predisposing factors*

Pregnancy during "delay" . . . . .	9
Chronic respiratory infections . . . . .	7
Fatigue in soldiers . . . . .	3
Allergy . . . . .	2

parent exposure to the fluorescent powder. For this reason, the designation, delayed chemical pneumonitis, suggested by Aub, has been adopted for use in this study. The delayed onset of the appearance of this syndrome is in contrast to the onset of acute chemical pneumonitis reported by Van Ordstrand (12) as an alleged manifestation of beryllium poisoning. In the latter condition symptoms and signs of acute chemical pneumonitis begin while the patient is actively engaged in working with beryllium compounds and disappear when he is removed from the industrial atmosphere.

*Incidence in relation to beryllium exposure:* In the present series of 36 cases of delayed chemical pneumonitis, there were 1,400 workers thought to be similarly exposed. There is insufficient information available as yet to interpret this low case incidence. Possible predisposing factors were chronic respiratory infections in 7 cases; pregnancy during the period before onset in 9 cases; and war fatigue in 3 soldiers (table 2). These 36 workers had been engaged in fluorescent lamp

manufacture for periods ranging from eight months to eight years. It is impossible to correlate the length and intensity of exposure in more or less hazardous positions with either the time of onset of the disease or the severity of the clinical picture.

*Symptoms:* The development of the disease was gradual in all cases. The patients sought medical advice in most instances (table 3) because of weight loss and fatigue, followed by gradually increasing exertional dyspnea with or without cough. Anorexia and nervousness were prominent at onset, especially among the women workers. Frequently a mild coryza failed to disappear; and when fatigue, weight loss, dyspnea on exertion and cough became persistent, the patient sought help. There were several unusual onsets (table 4) including 2 cases simulating Graves' disease, and 3 which presented the picture of rheumatoid arthritis.

TABLE 3  
*Symptoms at onset*

Weight loss .....	33
Dyspnea .....	32
Anorexia .....	32
Cough .....	21
Weakness and fatigue .....	18

TABLE 4  
*Syndromes at onset*

Persistent respiratory infection with weight loss .....	8
Graves' disease .....	2
Rheumatoid arthritis .....	3

*Roentgenologic findings:* Chest roentgenograms obtained during the onset periods revealed characteristic features which were common to the entire series. The roentgenologic picture of bilateral widespread involvement of the lungs in delayed chemical pneumonitis is striking and has not been previously observed. In a former report from this department (16) Sosman and Wilson described the roentgenologic changes in delayed chemical pneumonitis as taking place in three stages. The first stage suggests in their words "a sand storm," extending to the periphery and including the apices. The second stage is characterized by an increase in the hilar shadows and "a diffuse reticular pattern on a granular background." Finally, they describe a picture with small distinct nodules, which gives the lungs a "snow storm" appearance. In the present series, emphysematous changes at the apices, frequent midzonal distribution of density and 4 instances of small but distinct areas of spontaneous pneumothorax have been noted.

*Physical examination:* The findings on physical examination (table 5) in cases of delayed chemical pneumonitis have not been striking. Because of the weight loss and dyspnea, which was serious in most instances, the patients presented a miserable and characteristic appearance. There was very little elevation in tem-

perature, except in terminal episodes or during episodes of intercurrent respiratory infections. Inconstant auscultatory signs were the rule. Clubbed fingers were reported in 5 cases and cyanosis was definitely noted in only 8 instances. The liver was enlarged in 3 instances; the spleen in 3. Lymphadenopathy was reported as present in 3 patients and thyroid enlargement twice. In the more seriously ill group, 6 patients developed right-sided heart enlargement. Skin lesions, single and multiple, transitory in occurrence, nodular in type, were recorded in 4 cases.

*Laboratory studies:* The laboratory studies done on this series of cases is by no means complete. Sufficient material is available, however, to report that, in delayed chemical pneumonitis, smears and cultures of the sputum have failed to reveal tubercle bacilli. Cultures of blood and sputum for other pathogenic organisms have also been negative. Secondary polycythemia has developed in 3 cases, but otherwise the blood elements showed no change. Sedimentation times showed little change. Slightly elevated blood globulin, blood calcium and

TABLE 5  
*Physical findings*

Abnormal auscultatory signs .....	20
Cyanosis.....	8
Cardiac changes.....	6
Clubbing.....	5
Skin lesions.....	3
Enlargement of spleen.....	3
Lymphadenopathy .....	3
Thyroid enlargment.....	2
Enlargement of liver.....	2

alkaline phosphatase levels were detected in a few of the most seriously ill patients. In one instance the elevated blood calcium was associated with the passage of a kidney stone. Vital capacity studies as done in hospitals are notoriously rough indices of pulmonary function. As might be anticipated, however, in all cases of delayed chemical pneumonitis, where an effort was made to test the vital capacity, it was found to be diminished.

*Treatment:* Administration of oxygen has played a useful rôle in the treatment of the acutely ill patients in this series. Patients well enough to travel believe they have been benefited, probably through freedom from intercurrent respiratory infections, by trips to Florida and Arizona. The arsenicals, the sulfonamide compounds, penicillin and cytochrome-C have been tried on patients suffering with delayed chemical pneumonitis without notable success. To keep the patients' morale high has been a real problem; in part because of the ceaseless dyspnea, in part because these patients know of the death of their fellow workers and feel keenly the air of mystery which has surrounded the origin of this disease.

*Course of illness and complications:* On the basis of present experience, the 36 cases of delayed chemical pneumonitis have been arbitrarily divided into categories according to the observed severity of the course of the illness (table 6).

The severe group was comprised for the most part of patients who appeared chronologically earliest in the series. The complications occurred in this group. Weight loss up to 40 pounds in the first year of illness, dyspnea and orthopnea producing respiratory rates up to 60 times a minute were characteristic. Profound anorexia with nausea and vomiting at times was a part of the clinical course. Of the severe group, 6 have died after periods of illness varying from eight months to just over two years. One patient in this group has become completely well clinically and by roentgenogram after an illness of nearly three years.

Fourteen cases have been classified as moderately severe. The clinical course in these patients has been characterized by weight loss up to 25 pounds and dyspnea up to an average respiratory rate of 30. In addition, anorexia in the early

TABLE 6  
*Clinical Types of delayed chemical pneumonitis*

Severe.....	13 (6 deaths)
Moderately severe.....	14
Mild.....	5
Asymptomatic.....	4
Total.....	36

TABLE 7  
*Complications during the disease*

Acute respiratory infections.....	7
Congestive heart failure.....	3
Pregnancy (after onset).....	3
Emergency surgery.....	2
Renal calculi.....	2

stages of the illness and vomiting as a sequel to the bouts of coughing occurred regularly.

The 5 cases designated as mild had less than 10 pounds in weight loss, little or no cough, no gastro-intestinal symptoms and dyspnea only on exertion. The roentgenologic findings and occupational histories of these cases permitted their inclusion in the series of delayed chemical pneumonitis.

The 4 workers who are asymptomatic were exposed to beryllium compounds at the same time as the clinically ill workers and, like them, revealed the characteristic findings on routine roentgenologic examination of the chest.

*Prognosis:* Delayed chemical pneumonitis is shown by these data to be usually a severe illness of long duration. The duration, course and outcome of the disease were influenced unfavorably by the complications here listed. All patients reported that the slightest intercurrent respiratory infection increased the degree of dyspnea and, if present, the cough and sputum. In the five years of observation of these cases, the prognosis appears to be improving in that all of the 6 deaths occurred in the first 17 cases. The case mortality rate for the total of 36



cases here recorded is 17 per cent. Of the whole group of 36 cases of delayed chemical pneumonitis, 23 patients are still functionally disabled; 12 completely and 11 partially so after an average illness of two years. The 3 cases referred to as still convalescent but well enough to work had an average illness of eighteen months. Four cases as mentioned are free from symptoms, although presenting the characteristic roentgenologic changes.

"*Neighbor cases:*" Three instances of what appear to be true cases of delayed chemical pneumonitis in individuals who were *not* workers deserve mention because of the public health aspect of this industrial health problem. All 3 of these patients presented the characteristic clinical and roentgenologic findings of the syndrome and in 2, the diagnosis was confirmed by autopsy. These so-called "neighbor cases" were discovered in two patients who lived geographically very close to the building where the fluorescent powders were being handled. The third case is that of the mother of one of the workers who died after nearly two

TABLE 8  
*Status of patients—March, 1947*

Deaths.....	6
Disabled.....	23
Completely disabled.....	12
Partially disabled.....	11
Convalescent (working).....	3
Asymptomatic.....	4
Total.....	36

years of a severe course of delayed chemical pneumonitis. The mother, now a patient, was in constant nursing attendance on the fatally ill worker daughter.

*Histopathology:* Four of the worker cases and the 2 "neighbor cases" of delayed chemical pneumonitis were autopsied. The pathologists, in general, agree that the picture is one of an unusual type of severe granulomatous reaction which replaces normal tissue and chiefly involves the lung but also is present in the hilar nodes and the liver. The histology varies with the length of time the patient lived with the disease. In one case with a violent and shorter than average course, the process resulted in a marked emphysematous reaction and diffuse extensive cellular replacement of normal lung tissue. In another patient, who lived a year and a half longer with the disease, there was a more regular granulomatous formation with giant cells and considerable hyaline fibrosis.

The late Dr. Leroy Gardner of Saranac Lake, who studied the pathology of delayed chemical pneumonitis extensively, preferred to call it "diffuse pulmonary granulomatosis." At the time of his death, he was attempting to establish the etiology and the pathogenesis of delayed chemical pneumonitis by reproducing the disease in animals, using a variety of beryllium compounds introduced by vein and inhalation. Dr. Gardner had made much progress. The Trudeau Founda-

tion is carrying on the studies, but this and many other industrial investigations are at a great loss without this careful worker.

*Differentiation from other pulmonary diseases:* From the material presented, it is evident that, in making a diagnosis of delayed chemical pneumonitis, the roentgenologist must consider many etiologic possibilities which might produce such an unusual roentgenographic picture. The clinician must exclude the presence of pulmonary tuberculosis, Boeck's sarcoid or silicosis. A tuberculous infection is eliminated by the negative studies for the presence of the bacilli, plus the almost complete absence of fever in delayed chemical pneumonitis except as a terminal episode. Boeck's sarcoid may be excluded by the severe clinical course and poor prognosis. Also, there have been no bone changes discovered by roentgenogram in this series, and the occupational history points to a unique and common etiology. The roentgenologists who have reviewed the chest films from the present series do not believe that silicosis is the cause of the abnormal findings. Moreover, the autopsy findings of delayed chemical pneumonitis are unlike the well-described pathology of silicosis. The amount of silica in the lung ash of fatal cases of delayed chemical pneumonitis is not above that found in normal tissues, whereas in silicosis abnormal quantities are detected. Clinically, silicosis is not characteristically so severe until very late in the disease, and death usually occurs after superimposed acid-fast infection.

*Other cases of delayed chemical pneumonitis:* Since the earlier report (16) of 17 cases of delayed chemical pneumonitis in March, 1946, the occurrence of respiratory illness in several other groups of workers handling beryllium has been brought to the writer's attention. In one research laboratory there have been seven cases, apparently of acute chemical pneumonitis, with no deaths (19). Moreover, there are many scattered cases reported from the beryllium industry of acute chemical pneumonitis of the variety described by Van Ordstrand, where removal from the working environment results in clinical cure. In one metal-lurgy firm Jackson (20) has observed 7 cases with 5 deaths. It is believed that workers had been exposed to beryllium oxide in small amounts over a long period of time. The writer has also been informed of a few cases of workers who, despite recovery from acute chemical pneumonitis following exposure to the beryllium compounds, continued on a chronic course of pulmonary disability. In others, like the patients in the present report, the onset apparently occurred at a time remote from industrial exposure to a beryllium compound. With the present lack of a satisfactory quantitative test for beryllium in the air, industrial hygiene chemists and engineers are not yet ready to help settle definitely the etiological relationship between the worker's exposure to a beryllium compound and his clinical illness. It should be emphasized, therefore, that at the present time the incrimination of beryllium rests solely on its presence as the common denominator in the working environment of these patients who present various clinical types of pulmonary disability.

#### SUMMARY

The pertinent material from the clinical records of 36 workers exposed to beryllium compounds has been presented in an attempt to bring out the epidemiology

and chief clinical features of an apparently recently recognized occupational illness, which has been designated delayed chemical pneumonitis.

1. The distinctive clinical features of the disease are: a usual delay in onset, dramatic weight loss and dyspnea and long duration of illness. There is usually a history of remote exposure to beryllium compounds.

2. In each case it is necessary to exclude pulmonary tuberculosis, silicosis or sarcoidosis as a cause of the illness.

3. The etiology and pathogenesis of delayed chemical pneumonitis have not yet been clearly established. From experience with occupational illness and from experimental studies, evidence is accumulating which tends to incriminate beryllium compounds.

4. Instances of delayed chemical pneumonitis, as well as the acute chemical pneumonitis previously recognized, are appearing in various parts of the U. S. A. where workers are exposed to beryllium compounds.

#### SUMARIO

##### *Neumonitis Química Tardía en los Obreros Expuestos a los Compuestos del Berilio*

Tratando de exponer la epidemiología y principales características clínicas de una enfermedad profesional aparentemente descubierta hace poco y denominada por la A. neumonitis química tardía, preséntanse datos tomados de los protocolos clínicos de 36 obreros expuestos a los compuestos del berilio.

1. Las características clínicas distintivas de la dolencia son: retardo habitual en su iniciación, pérdida teatral de peso y disnea y prolongada duración del mal. Suele haber antecedentes de exposición remota a los compuestos del berilio.

2. En todos los casos se necesita un diagnóstico diferencial que excluya tuberculosis pulmonar, silicosis y sarcoidosis de Boeck.

3. Todavía no se han establecido netamente la etiología y patogenia de la neumonitis química tardía, pero se van acumulando datos derivados de la observación de enfermedades profesionales y de la investigación experimental que inculpan los compuestos del berilio.

4. Hay datos de que van apareciendo en varias partes de los E. U. A. donde los obreros se hallan expuestos a los compuestos del berilio, casos de neumonitis química tardía, así como de la neumonitis química aguda, previamente descrita.

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## DISCUSSION

GEORGE W. WRIGHT<sup>3</sup>

We have been interested in aspects of this interesting clinical phenomenon other than those so ably presented by Dr. Hardy. Dr. Gardner and his coworkers have explored a number of avenues designed to shed light on the etiology. Thus far they have been completely unable to reproduce the type of histological abnormality observed in those patients who have come to autopsy. Beryllium in a number of combinations and physical states has failed to produce the disease in experimental animals. It would appear important, therefore, to reserve the indictment of beryllium as the offending agent even though it is strongly suspect on the basis of its high correlation in exposure histories. Although additional extensive study of beryllium, either alone or in combination, still needs to be made, too confining attention to this element may delay discovery of other possible factors. The fact that many persons exposed to identical beryllium combinations fail to develop the disease strongly indicates that one or more additional agents may be acting. The term "delayed chemical pneumonitis" does not seem to us to be clearly appropriate since the disease has not been proven to be chemical in origin. Moreover,

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there is as yet no clear evidence that this disease is related to the acute chemical pneumonitis described by Van Ordstrand and others. We have no fitting term to suggest in the place of that now used. If the pathological lesion were better understood, a term descriptive of the histological picture might be appropriate. It would perhaps be better to refer to this disease as industrial pulmonary granuloma or sarcoid. Our own studies have been chiefly concerned with the pathological physiology and the differential diagnosis of this disease. We have evidence clearly indicating that in those suffering from severe dyspnea, an impediment to the passage of oxygen across the alveolar membrane is characteristic. In very severe and extensive lesions there is, in addition, a loss of breathing reserve. We have not studied the disease in its minimal and asymptomatic stages. While the differential diagnosis may not be difficult in those industrial plants harboring more than one case, it will be extremely difficult in isolated cases. We have a man now under observation who fits perfectly the roentgenologic, clinical and physiological requisites, but who represents an isolated instance in a plant that has no demonstrable beryllium exposure. A larger experience with greater knowledge of the variations of the clinical aspects of early and late stages will be essential in order to avoid an erroneous diagnosis.

# ALUMINUM THERAPY IN ADVANCED SILICOSIS<sup>1,2,3</sup>

JOHN W. BERRY<sup>4</sup>

## INTRODUCTION

In Colorado, mainly because of the extensive mining carried on in this state, silicosis is an important problem. As a consequence the report of Crombie, Blaisdell and MacPherson (1) of the use of aluminum powder as a treatment for silicosis occasioned great interest. These investigators observed improvement in 55 per cent of a group of 34 silicotic persons who received aluminum powder by inhalation. Thirty-three per cent of the group also showed improvement in pulmonary function, as measured by very elaborate methods. An attempt was made to control this experiment by the observation of an additional group of silicotic persons who received no aluminum powder. At comparable periods, the pulmonary function in the treated and in the control group was measured. This control system is probably inadequate because members of the control group had not been subjected to the same suggestive inhalations as were the members of the treated group. Nevertheless, 12 per cent of the controls experienced improvement as measured by the pulmonary function tests. Treatment of silicosis with aluminum powder was undertaken by Crombie, Blaisdell and MacPherson because they believed that the disability of silicosis was not due to the fibrotic lesions, but rather to a thickening of the alveolar membrane caused by liberation of an irritant from the silicon contained in the lung. Other workers (2, 3) had shown that the inhalation of aluminum powder would cause the regression of immature silicotic nodules in experimental animals.

This study of the treatment of human silicosis by the inhalation of aluminum powder is based upon the original work of Denny, Robson and Irwin (2, 3) in which it was demonstrated that finely divided aluminum powder would prevent the development of silicosis in animals which had been exposed to amounts of silicon adequate to produce silicosis. Denny and his associates had shown that the effect of aluminum in the prevention of silicosis was caused, in a large part at least, by the formation of an insoluble coating of gelatinous aluminum hydroxide about the particle of silicon. This coating prevented the solution of silicon and, presumably through this mechanism, prevented the development of silicosis.

<sup>1</sup> From the Department of Medicine and Division of Industrial Medicine, University of Colorado Medical Center, Denver, Colorado.

<sup>2</sup> The suggestion that led to this project was originally made by the late Mr. Donald E. Cummings. Mr. Cummings was the first director of the Industrial Hygiene Division of the Department of Medicine, University of Colorado Medical Center.

<sup>3</sup> Presented before the Medical Section, as part of the symposium on *Pulmonary Diseases in Industry*, at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 19, 1947.

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Gardner, Dworski and Delahant (4) also demonstrated that aluminum would protect animals against silicosis and, in 1944, reported improvement in the symptoms and pulmonary function of 2 of 7 silicotics treated with aluminum. They expressed considerable doubt, however, as to whether aluminum was responsible for the improvement which was observed in their patients.

By far the best results in the treatment of human silicosis with aluminum are those reported by Hannon (5). In one group of 33 patients, all disabled by silicosis, he noted improvement in 100 per cent following the inhalation of aluminum powder. These patients were selected because silicosis was the only disabling disease present. Another group reported by the same investigator consisted of 247 persons with roentgenologic evidence of silicosis. Of these, 143 had some degree of disability and, of this disabled group, 94 per cent were improved following treatment. Of those without disability, approximately 90 per cent showed improvement. These men were all treated with metallic aluminum powder.

Johns and Petronella (6) have also reported improvement in 56 per cent of a group of 75 patients treated with aluminum. None of their patients were disabled.

The above reports, with one exception, describe the results of the treatment of silicosis with metallic aluminum powder. Gardner and his associates had used amorphous aluminum hydrate in their studies. Bamberger (7) conducted experiments in an effort to compare the results obtained by these two aluminum compounds. Forty-three per cent of those treated with hydrated alumina were improved, while 30 per cent of those treated with metallic alumina were improved. There was no objective improvement in any of Bamberger's cases, and they were not disabled prior to treatment. He felt that, because of the small number of cases, he was not justified in forming any conclusions.

This brief review of published studies presents the status of the aluminum therapy of silicosis at the time the present investigation was started. On the basis of these reports it would seem that: (1) many silicotics have apparently been relieved of their symptoms and, to a certain extent, their disability by the administration of aluminum; (2) two compounds are apparently effective—freshly ground metallic aluminum, which after grinding is about 80 per cent aluminum oxide and 20 per cent metallic aluminum, and amorphous hydrated alumina (XH-1010); (3) most of the reported improvement has been subjective, although a fair number of patients have shown improvement in pulmonary function by objective measurement; (4) there have been no satisfactorily controlled experiments; and (5) the optimum dose of aluminum has not been determined.

Thus it appeared that there was no real proof that the inhalation of aluminum produced significant improvement in silicotics. The reported improvement for the most part has been subjective and the possibility of improvement in pulmonary function in advanced silicotics may justifiably be questioned. Accord-

ingly, it was decided to undertake a controlled study of the effect of aluminum in advanced silicosis.

#### PLAN OF INVESTIGATION

*Administration of the aluminum:* Consideration of the methods of administering the aluminum dust in the previous studies led to the conclusion that none of the available methods produced a constant concentration of dust. As a result the dose could only be approximated. Consequently the help of the engineering staff of the Industrial Medicine Division of the Medical Center of the University of Colorado was sought to produce an apparatus which would deliver a constant known quantity of aluminum dust. Such an apparatus was designed and constructed by Ingram and Church (8) (figure 1). This machine produces a dust concentration that can be controlled within plus or minus 10 per cent. The dust concentration cannot be regulated more precisely because the powder used is hygroscopic, so that the concentration varies with the atmospheric humidity. Moreover, the tube is filled by hand, making it difficult to produce the same density of powder each time it is filled. The latter difficulty can be easily overcome by filling the tube with a weighed amount of dust in a known volume. This is contemplated for the future.

*Aluminum preparation:* The powder used in the study has been hydrated alumina, identified as XH-1010, supplied to us by Dr. F. C. Frary of the Aluminum Company of America. The material is a very fine white powder and 90 per cent of the particles are under 3 micra in diameter. It has a slight taste and odor which are not objectionable.

Hydrated alumina was chosen for several reasons. It does not flocculate on contact with body fluids, as does the metallic aluminum powder. Bamberger's (7) work suggested that amorphous alumina was perhaps superior to the metallic aluminum powder, and Gardner (4) had pointed out that hydrated alumina was probably the inhibitory substance ultimately produced by solution of the metallic aluminum in the body fluids of the living animal. Hydrated alumina is stable and, therefore, a mill to grind it is not necessary. Finally, hydrated alumina lends itself better to a controlled experiment, as it is a white powder, and the controls would therefore be less likely to detect the absence of dust in the atmosphere they breathe. When metallic aluminum is used, the tongue and oral tissues are stained black, as is the sputum, for considerable time after the inhalation of the powder.

In this study, the concentration of dust has been 300,000,000 particles per cubic foot of air. This amounts to one mg. per cubic foot. This dose was arbitrarily chosen, as there was no standard by which to judge the proper dose. It is as large or slightly larger than the doses used by other investigators.

*Experimental subjects:* The patients have been selected with several qualifications in mind: (1) the absence of proved, active tuberculosis; (2) the presence of disability in most patients; (3) willingness on the part of the patient to give sufficient time for adequate treatment; (4) the absence of compensation factors which would tend to color the patient's symptoms.



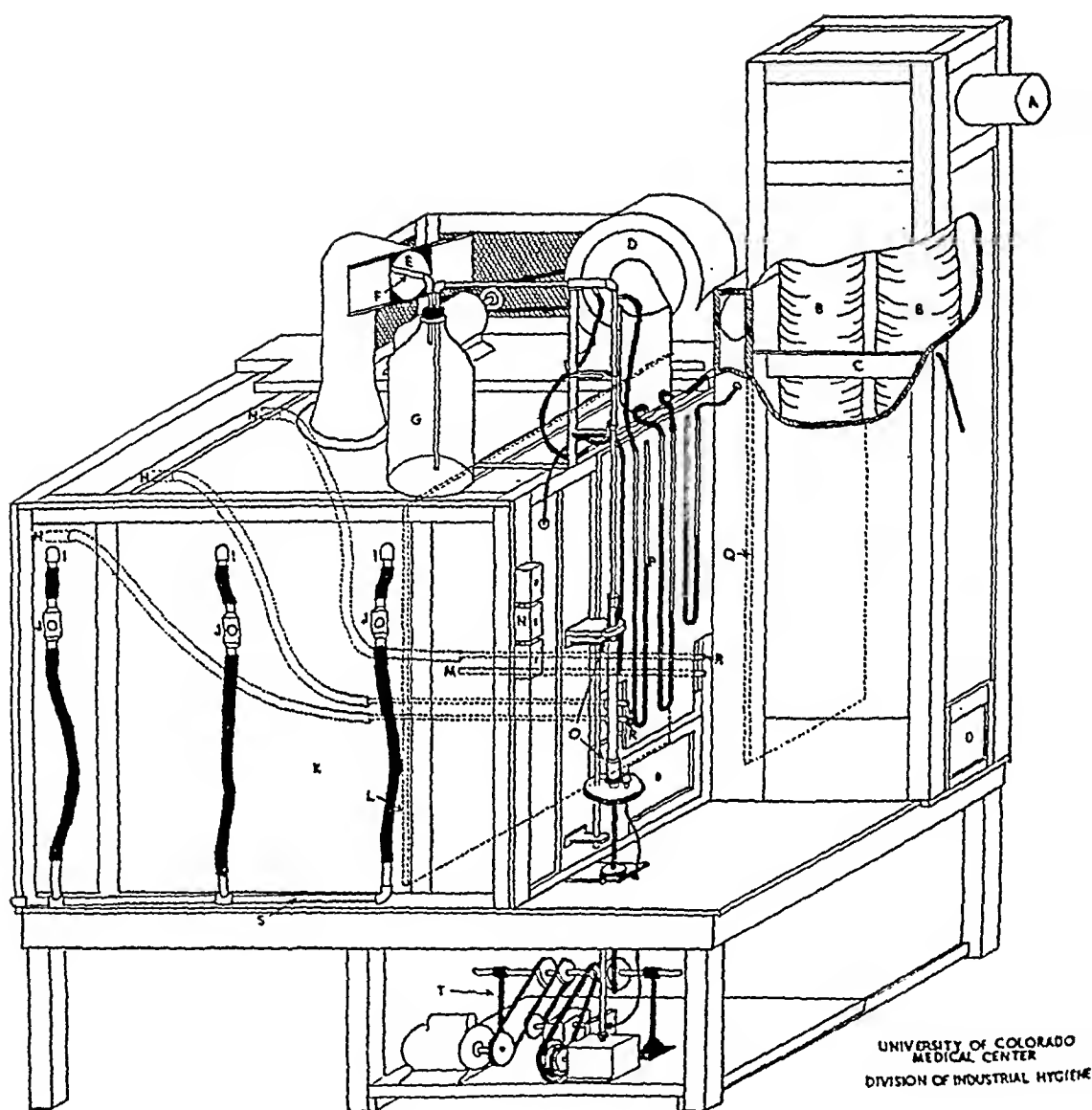


FIG. 1. A: Exhaust vent leading to outside. This carries the aluminum that is contained in the expired air of the patient and the air that has traversed the chamber, after it has been cleaned of the aluminum. B: Filter bags by means of which aluminum powder is reclaimed. C: Agitator by means of which dust is gathered at the bottom of the bags. D: Large blower by means of which the atmosphere within the box is continuously and rapidly changed. This avoids dilution of the dust content in the box by the patient's inspiration. E: Main intake for chamber. F: Tube by means of which the fine aluminum powder is admitted into the chamber. G: Large settling chamber wherein large particles of aluminum settle out. H: Outlets from which the control patients breathe. It may be seen that tubes traverse the box (these were concealed from the patient's view) and draw air free of aluminum from the intake ports marked R. I: Outlets delivering the dusty atmosphere contained within the chamber to the patient; on the opposite side of the box there are three similar outlets which deliver dust-containing air. J: Two-way diaphragm valve which guides the air stream from the box to the patient to the contaminated dust outlet, which is marked S. In this way, no

The treated group consisted of 26 men and the control group of 9.<sup>6</sup> The examination of both groups has been exactly the same and, until this report was prepared, the investigator did not know which men were controls and which were being treated.

*Pre-treatment studies:* The preliminary examination consisted of: a history, with special emphasis on occupation; a physical examination; a complete blood count; hematocrit; urinalysis; sedimentation rate; determination of vital capacity; and an electrocardiograph with six chest leads. It has been impossible thus far to perform the more detailed pulmonary function tests.

Six separate sputum specimens were examined for tubercle bacilli by concentration and smear. If the smears were negative, a guinea pig and culture were inoculated. Sputa were considered negative for tubercle bacilli only when the results of the guinea pig inoculation and the culture had been reported as negative. Patients were included in the study when the guinea pig and culture were negative unless there was very strong clinical evidence of pulmonary tuberculosis. Because of the well known difficulties in establishing the presence of active pulmonary tuberculosis in a patient with silicosis, these procedures probably do not rule out all cases of tuberculosis complicating silicosis. Unfortunately, however, in such a situation there is no other practical and reasonable method of excluding the presence of active tuberculosis.

Follow-up studies were done at intervals of approximately two months, when the physical examination and the original laboratory tests were repeated.

*Treatment regimen:* The general plan of treatment has been to alternate four weeks of treatment with four weeks of rest. The men inhale the dust or, in the case of the controls, room air, twenty minutes per day, five days per week. An effort has been made to continue the treatment program for a total period of one year. For economic and other reasons, many exceptions have had to be made to this plan. The exceptions have been of two types: occasionally it would be

<sup>6</sup> The control group has been increased to a total of 16 men since this paper was originally presented at the annual meeting of the National Tuberculosis Association in San Francisco in June, 1947. The addition of these 7 men in no way changes the results as reported at the San Francisco meeting. Analysis of the course in these 7 shows that, without exception, they experienced considerable subjective improvement.

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contamination of the air within the chamber occurs. K: The dust chamber. This is a box, the dimensions of which are 4 x 4 x 4 feet. L: Baffle plate in the dust chamber which prevents uneven concentration of the dust. M: Tube by which samples of the chamber atmosphere can be obtained for dust counting. N: Electrical switches controlling the various motors activating the machine. O: The dust feed mechanism. It consists of a glass tube marked O, which is mounted on a platform; the entire platform rises at a constant speed while simultaneously rotating. Both of these actions are produced by means of the mechanism marked T. It can be seen from the drawing that there is a smaller tube leading from the dust containing tube up into the settling chamber. By means of a venturi valve, there is a vacuum in the portion of the tube that is in contact with the dust, and there is positive pressure in that part of the tube leading from the valve to the settling chamber. P: Manometers used to measure the pressure in various parts of the apparatus. Q: Baffle plate for filter bag chamber. S: As mentioned above, this tube carries the dust and the expired air of the patients directly to the outside of the building. (Diagram drawn by William A. McGilvray of the Division of Industrial Medicine.)

necessary to allow a man to continue treatment without rest in order that he could follow seasonal employment; or, conversely, it would occasionally be advantageous to the patient to allow him to take a prolonged rest period in order that he could undertake some employment.

During the course of the study two sources of error have been found which could conceivably have allowed the controls to receive some aluminum. The apparatus developed a leak in the exhaust chamber for a short period of time and may have contaminated the room. Simultaneous dust counts of the treatment room atmosphere and the atmosphere of the corridors of the hospital, however, failed to show any significant increase in the dust in the treatment room over that of the corridors. The chemical nature of the dust was not identified. The other possible source of error concerned the fresh air intakes. As these intakes for the control ports are located close to the cylinder containing aluminum, it would be possible for some contamination to occur. But again, dust counts of air samples from the control outlets and corridors of the general hospital did not show any significant differences. For these reasons, it is very unlikely that the control group received any aluminum.

*Duration of exposure to silicon:* The average time since the last exposure to hazardous concentration of silicon of the treated group is 3.2 years, and ranges from 0 to 10 years. The control group had been removed from silicon hazard for an average time of 4.4 years, with a range of 0 to 13 years. In each group, there was one man who had been away from a dusty occupation for a long period of time. The length of this period was ten years for the member of the treated group and thirteen years for the subject in the control series. If these 2 individuals be excluded, the average time away from a dusty occupation was 2.9 years for the treated patients and 3.2 years for the control group.

The members of the treated group have received an average of ninety-six days of actual treatment, and those of the control group fifty-five days of actual treatment.<sup>6</sup>

## RESULTS

Physical examination disclosed the usual findings in advanced silicosis. There was no significant change in the physical signs in any patient during the period of the study. In 2 of the patients, tubercle bacilli were found in the sputum after the start of the experiment.

The hematocrit was within normal limits in all members of the treated group before treatment. It rose to abnormal levels in 3 patients during the course of treatment or following treatment. One of these patients died and the others became clinically worse. In the control group, the hematocrit was within the normal limits before and during the course of the study.

Measurement of the vital capacity is known to be a very inaccurate method for determining pulmonary function. Nevertheless it was believed that perhaps some information might be obtained by doing serial determinations on these

<sup>6</sup> Since this paper was originally read, the project has been continued, so that now the average number of treatment days for both the control and the treated group is 120 days. This increase in the length of treatment has not changed the experimental results.

patients. The vital capacity was calculated on the basis of 2.5 liters per square meter of body surface representing the normal. The average vital capacity of the treated group was 74.5 per cent of normal, with a range of 43 to 119 per cent. The average vital capacity in the control group was 54 per cent, with a range of 42 to 90 per cent. During the period of the study, there were many minor variations in the vital capacity of these patients, but there was no significant improvement in either group.

The electrocardiogram was abnormal in approximately 75 per cent of each group, when judged by very rigid standards. The abnormal changes in most instances were very minor, and could in no way be attributed to silicosis. In a few cases, however, there was a typical right ventricular strain pattern. As the present report is concerned only with the effects of treatment on these patients, it is sufficient to note that significant electrocardiographic changes appeared in only one patient, a man with an anterior myocardial infarction.

*Roentgenologic studies:* Roentgenologic study of the treated group revealed the massive conglomerate lesions of third stage silicosis in 96 per cent of the cases, and discrete nodulation in 4 per cent. In addition to the silicotic lesions, 73 per cent of the treated group had bullous emphysema. Two patients of the treated group showed roentgenologic evidence of progression of the disease while under treatment. In one member of the treated group regression of the nodular densities was observed. This man presented the nodular stage of silicosis. He had had six years' exposure in a dry quartz mine as a driller and his last exposure was six years prior to treatment. The evident clearing cannot be explained by technical difference in the roentgenograms as exposures have been made that would demonstrate any such difference. This man was not actually disabled by silicosis, and in retrospect it would seem that the diagnosis is open to question. Nevertheless several competent specialists have interpreted the roentgenograms as representing definite silicosis. In one other member of the treated group a very questionable decrease in the size of the nodules was observed.

Seventy-eight per cent of the control group had third-stage silicosis, and 22 per cent were in the second stage of silicosis. Eighty-nine per cent of the control group had bullous emphysema. One member of the control group has shown progression of the disease. No member of the control group has shown any regression of the lesions.

The presence of bullous emphysema in such a high percentage of these patients is to be expected, as bullous emphysema occurs in the majority of patients suffering from advanced silicosis.

*Symptomatic changes during treatment:* The principal symptoms studied were disability, dyspnea, cough and chest pain. These four symptoms were encountered most frequently, showed the greatest change and have received the chief consideration in previous reports.

In the present investigation each symptom has been arbitrarily classified as severe, moderate, or mild. A further subdivision of "severe" into "severe but improved," and "moderate" into "moderate but improved" has been made in order to denote minor degrees of improvement. The basis for the subdivision

varies with the particular symptom concerned and is explained in the discussion of that symptom.

The data regarding these symptoms are presented in figures 2 to 9. The figures are all arranged in a similar manner. Horizontal lines divide each figure into six parts which from above downward represent the symptomatic categories: severe, severe but improved, moderate, moderate but improved, mild, and none. The vertical lines on each figure indicate the time in months. The position of the points on the first vertical line represents the patient's status prior to treat-

### DISABILITY CHANGED TREATED GROUP

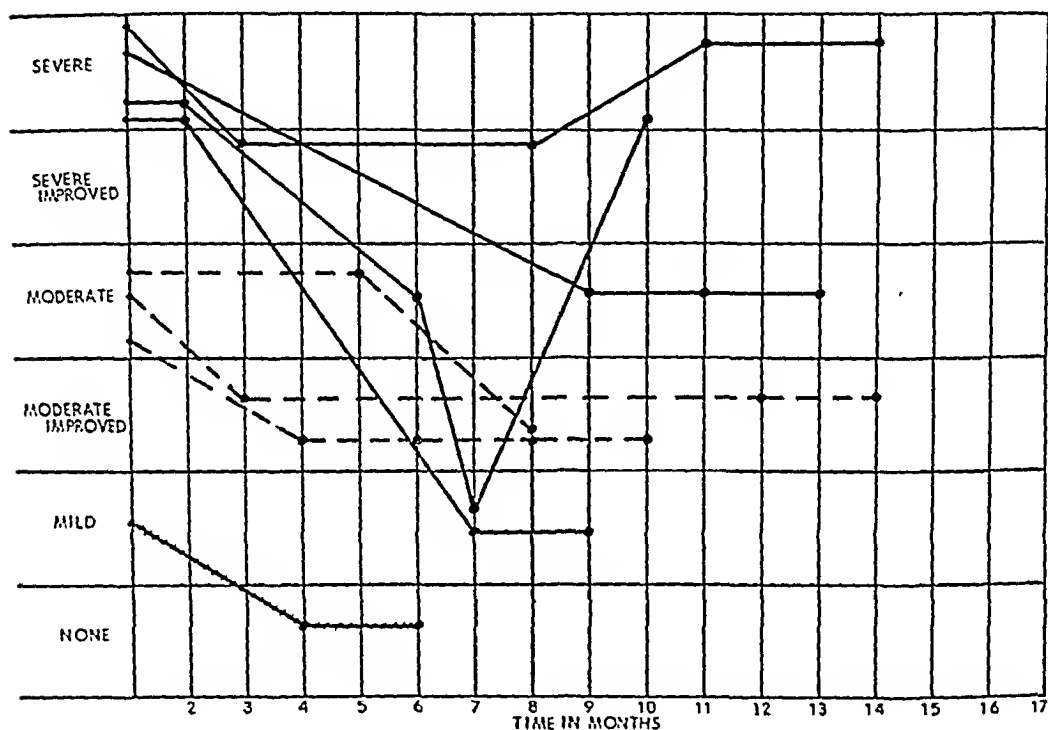


FIG. 2

ment, and the remaining points denote the patient's status at subsequent examinations.

Disability has been subdivided into degrees as mentioned above. The patients with severe disability were unable to work at any job; those with moderate disability were able to work at a job that was physically less exacting than their previous dusty occupation; those with mild disability were able to carry on their usual occupation, but with noticeable distress.

Ninety-six per cent of the treated group had some degree of disability: 54 per cent had severe disability; 38 per cent had moderate disability; and 4 per cent had mild disability.

During the course of treatment, 68 per cent of the treated group showed no change in the degree of disability.

The symptomatic course of the members of the treated group in whom there was a change in disability may be seen in figure 2. A total of 8 patients have shown improvement. Two of these patients have returned to their previous state of disability after varying periods of decreased disability, so that 6 have improved and maintained their improvement to this time. In only one patient has the improvement been sufficient to change the patient's classification. Of the patients with severe disability, 4 improved, but only 2 have maintained their improvement. Of those with moderate disability, 3 have improved and main-

## DISABILITY CONTROL GROUP

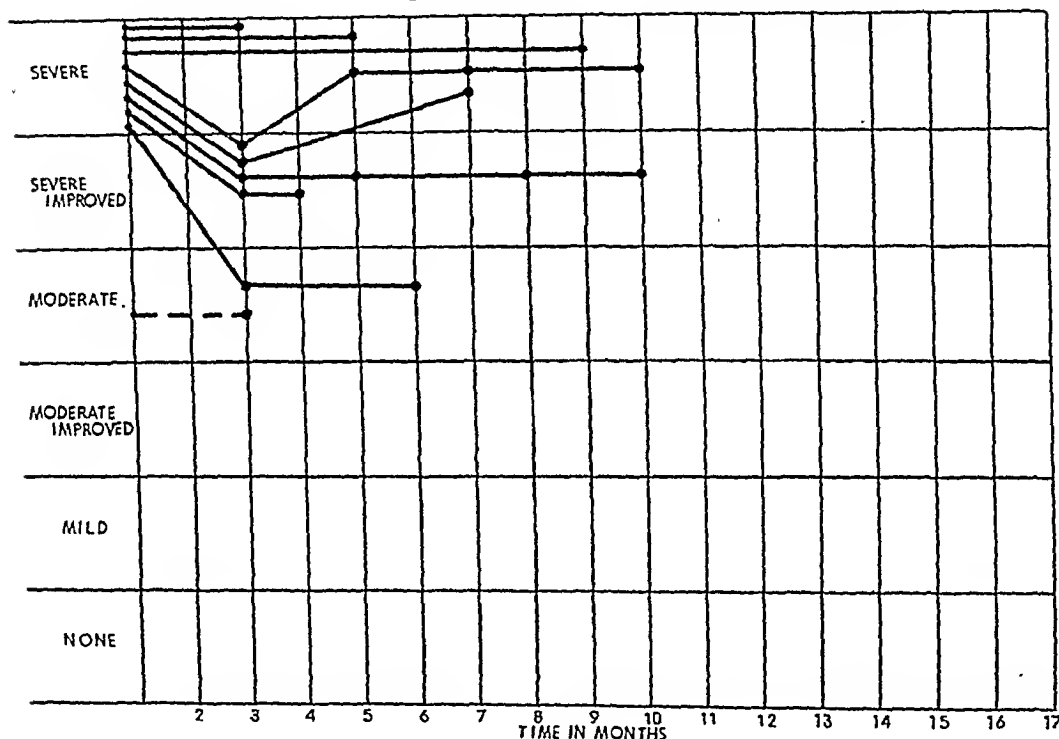


FIG. 3

tained their improvement to the present. The only patient with mild disability has improved and maintained his improvement.

The changes in disability which occurred among members of the control group may be seen in figure 3. Of this group, all had some degree of disability, and 6 patients experienced some improvement. Two patients have returned to their previous state of disability, leaving 4 who have improved and maintained their improvement to the present. One patient has achieved sufficient improvement to change his classification. Five patients with severe disability have improved, but in only 3 has the improvement been maintained.

Dyspnea has also been divided into several groups. The patients with severe dyspnea were unable to walk two blocks on level ground without stopping because of breathlessness. Those with moderate dyspnea could negotiate level

ground without stopping, but were unable to climb two flights of stairs without a pause. Those patients with mild dyspnea could climb two flights of stairs without stopping, but with noticeable dyspnea.

Ninety-six per cent of the treated group had some degree of dyspnea (figure 4). Fifteen patients of the treated group have improved, and 13 have maintained their improvement to the present time. Of the 9 patients with severe dyspnea, all improved and 7 have maintained their improvement to the present time. Of

### DYSPNEA TREATED GROUP

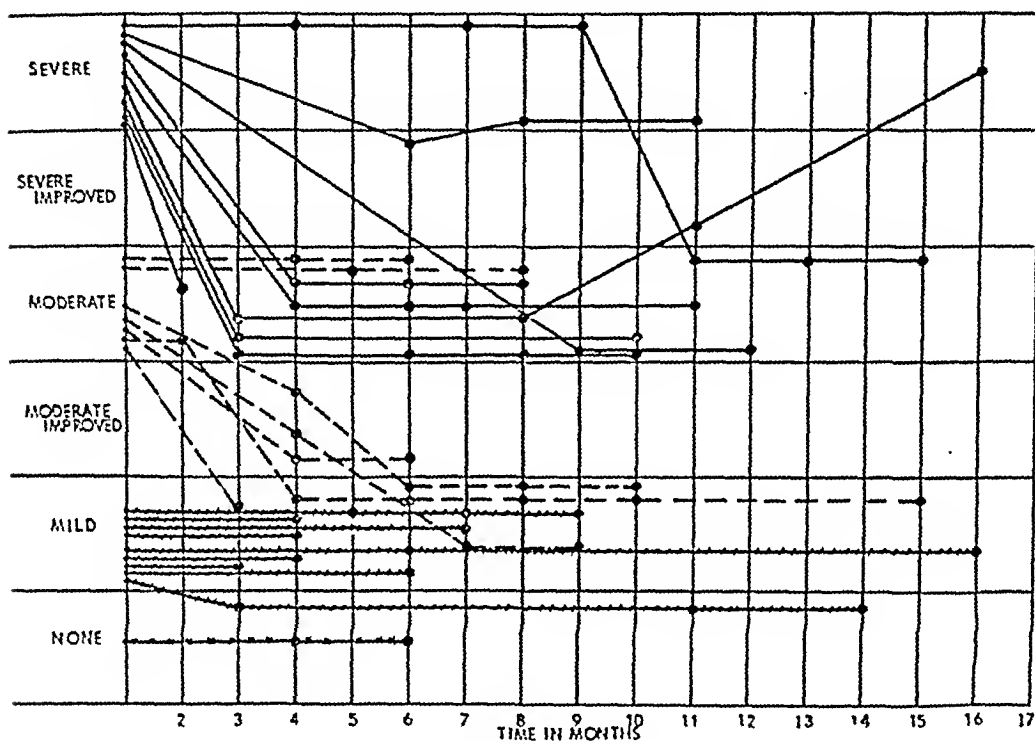


FIG. 4

the 7 with moderate dyspnea, 5 have improved and maintained their improvement. Of the 9 with mild dyspnea, one improved and has maintained his improvement to the present time.

All of the members of the control group had some degree of dyspnea (figure 5). Of those with severe dyspnea, 4 improved, but in only 2 was the improvement sustained. Both of the control subjects whose dyspnea was classified as moderate improved and have maintained their improvement.

Chest pain has been divided into three classifications: severe if it caused patients to lose sleep; moderate if it was one of the prominent complaints of the patient; and mild if it was a complaint elicited by direct questioning. Various sensations complained of by silicotics have been grouped together under the heading "chest pain." These include such symptoms as tightness, constriction, and actual chest pain, which is uncommonly of the pleural type.

Fifteen of the treated group had some degree of chest pain as may be seen in figure 6. Two patients who had no chest pain at the start of treatment developed this symptoms during the course of treatment. None of the treated group had severe chest pain; 8 had moderate chest pain and 4 of these improved and maintained their improvement. Of those with mild chest pain in the treated group, 5 improved and maintained their improvement.

In the control series, 4 patients had chest pain, and in each case it was moderate (figure 7). All 4 improved, but only 3 have maintained their improvement to the present time.

### DYSPNEA CONTROL GROUP

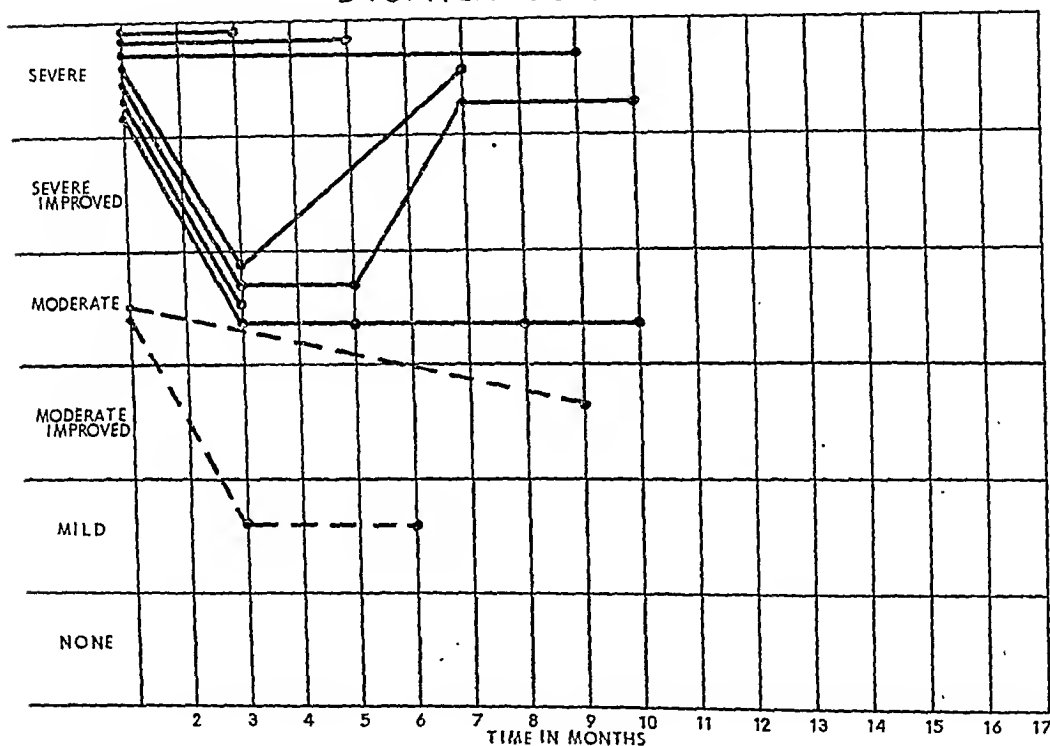


Fig. 5

Cough has been divided into three categories on the following basis: those with severe cough had a distressing cough which awakened them at least twice per night; those with moderate cough had a noticeable and frequently distressing cough during the day, but were awakened by cough only once or not at all during the night; those with mild cough had a frequent cough during the day, but no nocturnal cough.

All but 2 of the 26 patients in the treated group had cough to some degree (figure 8): 9 had severe cough; 5, moderate cough; and in 10 patients the cough was mild. Of the treated group 12 improved, and 9 have maintained their improvement. Of those with severe cough, 5 improved and maintained their improvement to the present. Of those with moderate cough, 3 have improved



# CHEST PAIN TREATED GROUP

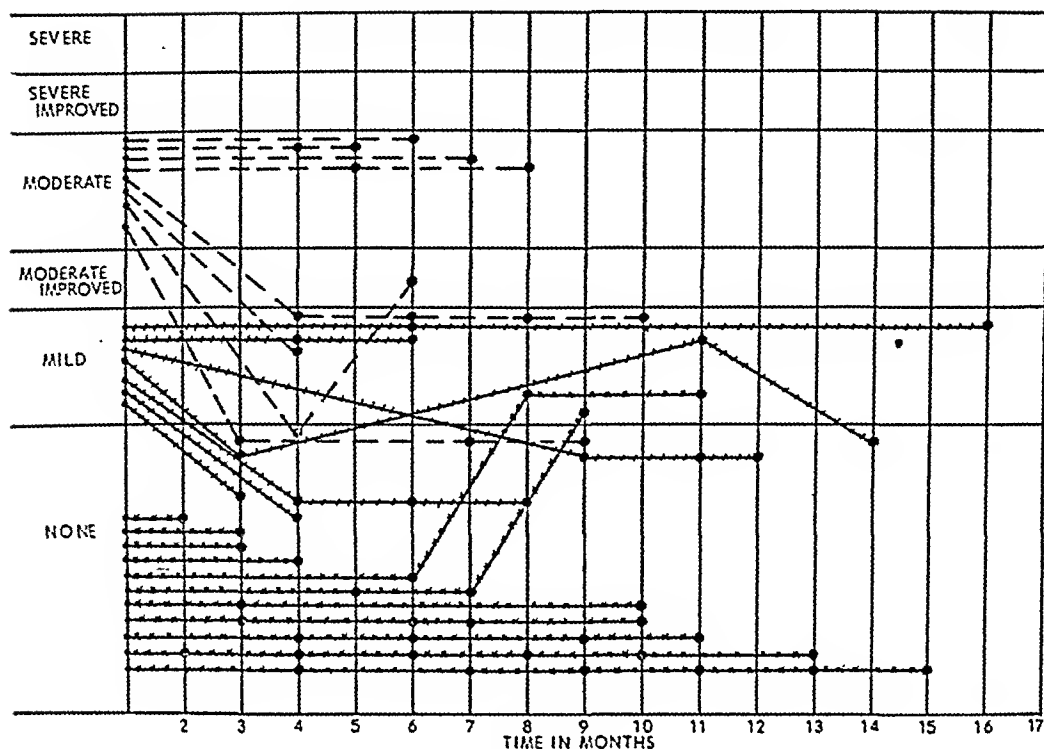


Fig. 6

# CHEST PAIN CONTROL GROUP

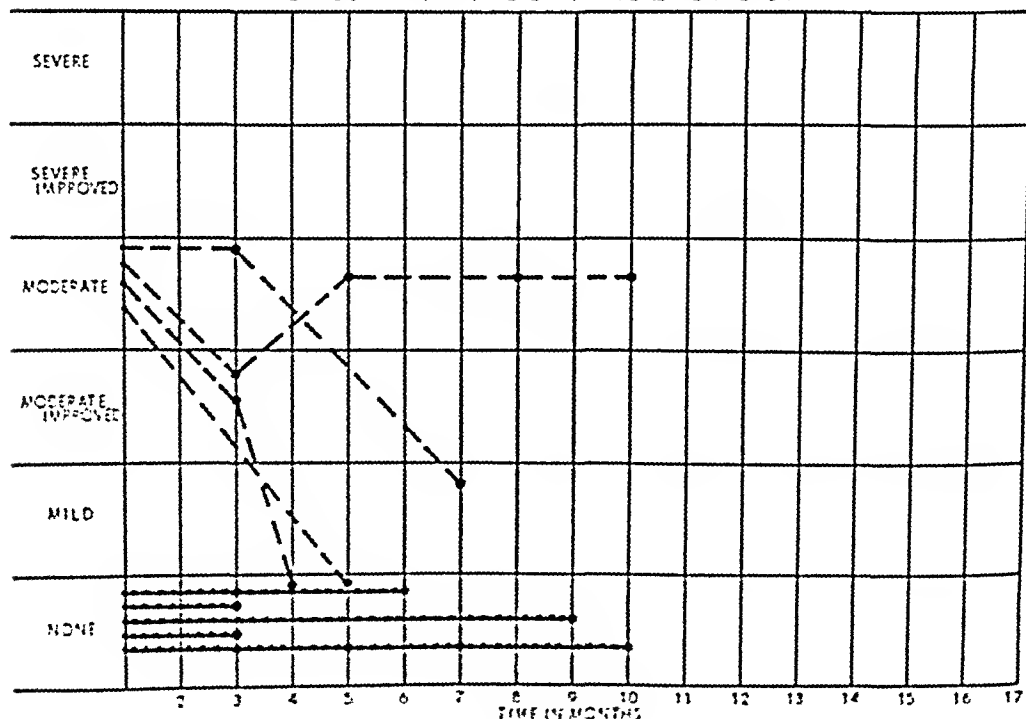


Fig. 7

# COUGH TREATED GROUP

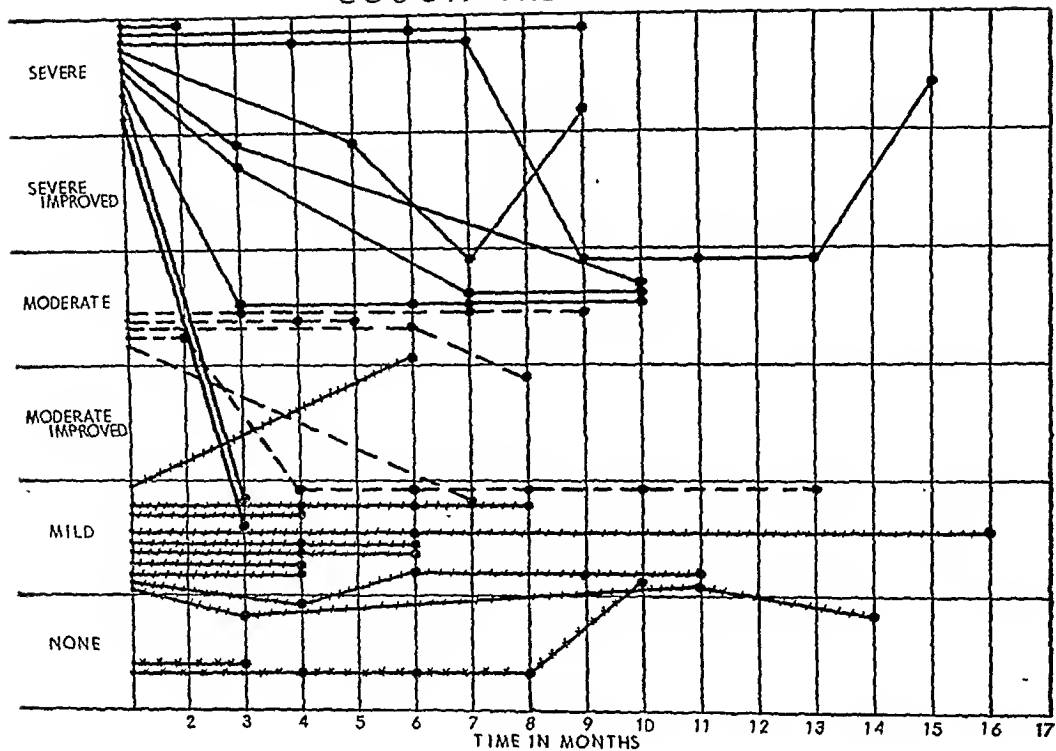


FIG. 8

# COUGH CONTROL GROUP

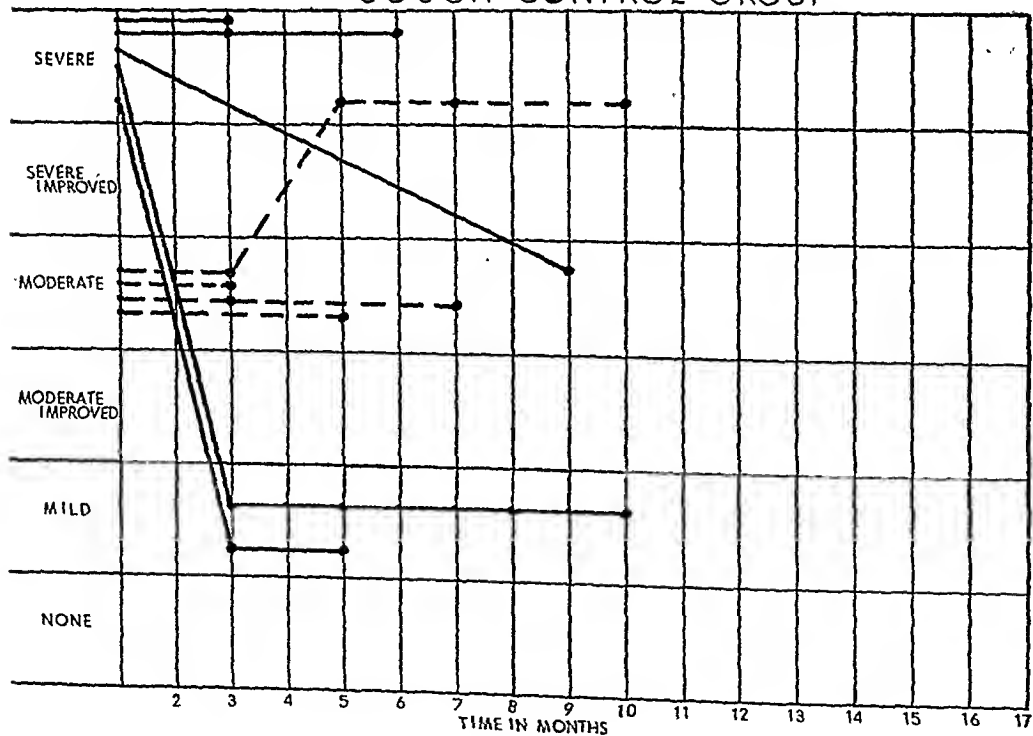


FIG. 9

and maintained their improvement. One of the patients with a mild cough has improved and maintained the improvement. Another became worse, and still another developed a cough during treatment.

All members of the control group had cough to some degree (figure 9). In 5 the cough was classified as severe, and in 4 it was only moderately severe. Of those with severe cough, 3 improved and maintained their improvement. Of those with moderate cough, none improved and one became worse.

The amount of sputum produced by these patients was reduced in a significant number of cases. Reduction occurred in both the treated and control groups.

Of the treated group, 85 per cent raised measurable amounts of sputum. The amounts as reported are not mathematically accurate, as no effort was made to

TABLE 1\*

*The symptomatic course of patients receiving aluminum, compared with the symptomatic course in those not receiving aluminum (control group)*

	IMPROVED		IMPROVED AND MAINTAINED		UNCHANGED		WORSE	
	Treated Group	Control Group	Treated Group	Control Group	Treated Group	Control Group	Treated Group	Control Group
Disability.....	32	67	23	44	68	33	0	0
Dyspnea.....	60	67	52	44	40	33	0	0
Chest pain.....	60	100	60	75	40	0	8	0
Cough.....	50	33	38	33	46	56	8	11
Sputum.....	55	56	55	56	36	33	19	11

\* Values represent percentage of those who had the symptom at start of treatment, with the following exception: Those who developed symptom during course of treatment are included in the group who became worse, and this figure therefore represents percentage of the entire group.

separate saliva and sputum. Approximately one-half of those who raised sputum showed a decrease in the daily sputum production. The most marked decrease was from 120 cc. to 4 cc. per day; the smallest decrease was from 8 to 4 cc. per day. Three patients of the treated group began to raise sputum for the first time during treatment, and 2 others increased the daily sputum production.

All members of the control group raised sputum and approximately one-half raised less sputum following treatment. The greatest decrease was from 60 to 4 cc. per day, and the smallest decrease was from 44 to 30 cc. per day. One patient raised more sputum following treatment.

A comparison of the findings in the treated and in the control group of patients is presented in table 1.

#### DISCUSSION

It was thought to be of interest to compare the investigator's impression with that of the patient in regard to improvement or deterioration in health. Of the

treated group, 22 considered themselves to have improved; 4 considered themselves to have been unchanged and none believed that they were worse. It was the impression of the investigator that 15 had remained unchanged, and that 8 had become worse. Three men, members of the treated group, undoubtedly became better. It is not possible to attribute all the improvement to aluminum, as each one of these men prior to treatment had been working in the dusty atmosphere of a hard rock mine, but during and following treatment had found other employment. It is well known that removal of a silicotic from a dusty atmosphere will by itself produce considerable subjective improvement.

All members of the control group considered themselves improved. It was the impression of the investigator that 6 were unchanged and 3 were worse.

During the course of the study, there has been no evidence of aluminum toxicity. This is of interest because there are several reports in the literature (9, 10, 11) concerning possible toxic effects of aluminum dust on the lung. In all of the reported cases, the aluminum concentration has been exceedingly high in the atmosphere breathed by the affected persons but there is as yet no convincing proof that aluminum was responsible for the changes observed.

During the course of this study, 2 of the patients discharged tubercle bacilli in the sputum for the first time. Both of these men were members of the control group. It should be emphasized that neither of these patients had received aluminum powder at any time for there is some evidence that inhalation of large amounts of aluminum powder may lower the native resistance to tuberculosis of guinea pigs (4).

The present study has been limited to observations on the disability and symptoms of advanced silicosis and has not been concerned with the use of aluminum in the prevention of silicosis.

Definite conclusions cannot be formed from a comparative study of such small series. Nevertheless, the high incidence of symptomatic improvement in the control series indicates that future work with aluminum in the treatment of disabling silicosis must be properly controlled in order that its worth may be proved. The results of the uncontrolled experiments reported to this time cannot be accepted as conclusive.

#### SUMMARY

A study has been made of the course of the symptoms of 26 silicotic patients who were treated with inhalations of aluminum dust and 9 patients with comparable degrees of silicosis who received no aluminum. The members of the latter group were treated with inhalations of room air but otherwise the management of the two groups was identical. All 35 patients were under the impression that they were receiving the same therapy. An impressive degree of subjective improvement was reported by the majority of the individuals in both groups. In the aluminum treated group, no objective changes were observed which could be convincingly attributed to the metallic therapy.

## SUMARIO

*La Aluminoterapia en la Silicosis Avanzada*

Este estudio versa sobre la evolución de los síntomas en 26 silicóticos tratados con inhalaciones de polvo de aluminio y en otros 9 que mostraban silicosis comparable y no recibieron aluminio. Estos últimos fueron tratados con inhalaciones del aire del cuarto, pero en lo demás la asistencia recibida por los dos grupos fué idéntica. Los 35 enfermos se hallaban bajo la impresión de que recibían la misma terapéutica. La mayoría de los individuos de ambos grupos comunicaron una imponente mejoría subjetiva. En el grupo tratado con aluminio, no se observaron alteraciones objetivas que pudieran imputarse convincentemente a la metaloterapia.

*Acknowledgments*

The author wishes to acknowledge the invaluable help and encouragement given us during the course of this work by the late Doctor Gardner of the Saranac Laboratories, Trudeau Foundation, Saranac Lake, New York.

The author also wishes to acknowledge the help of Dr. H. Lowry, who spent many hours analyzing the data on which this paper is based and devising a method of graphic presentation.

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## DISCUSSION

GEORGE W. WRIGHT<sup>2</sup>

Doctor Berry's study clearly portrays the tremendous problem of psychological effects of therapy; especially if the disease being treated is chronic and the patient is desperately

<sup>2</sup> Edward L. Trudeau Foundation, Saranac Lake, New York.

seeking relief. We obtained results of the same nature from a similar group of men in the varying grades of silicosis. Although roughly 40 per cent of our treated men claimed symptomatic improvement, careful physiological tests before and after treatment failed to confirm these claims. Less than 5 per cent of the men showed a measurable change for the better. We also treated a small number of men as controls who had no evidence of silicosis but who had had some exposure to free silica. These men suspected that they had silicosis and a high per cent claimed symptomatic improvement. It is very apparent that those investigators who claim remarkable improvement in a high percentage of silicosis cases treated by aluminum therapy have failed to pay sufficient attention to the psychological aspects of this form of treatment.

## THE CONTROL OF TUBERCULOSIS IN A MASS PRODUCTION INDUSTRY<sup>1</sup>

FRED B. WISHARD\*

The automotive industry, which is an excellent example of mass production on a large scale, has come to recognize the fact that, by the observance of a few simple rules, tuberculosis need no longer be considered a major health problem. In other words, the control of this disease may be handled as a part of the general health program of the industry.

Tuberculosis occurs in industry in one of two ways; by conditions incident to employment, or it may occur in the course of employment but not necessarily out of it. In the first instance, the employment must afford unusual opportunities for contact with the tubercle bacillus or there must be hazards which specifically increase the individual's susceptibility to this disease. In the second, the employee becomes infected outside his employment and goes on to develop an active lesion in spite of the most healthful working conditions. It can be truly said that occupational infection is extremely rare in the automotive industry, for the reason that an alert health program prevents employees from coming in contact with infectious cases on the job except for the short space of time prior to the case being discovered. During the past 15 years in one division of General Motors (2), with an average employment of 12,000, at no time have there been two cases of active tuberculosis in the same department in any one year, although some departments employ 300 or more persons, both men and women, in close proximity to each other, on conveyor belts, and the like. Nevertheless, an alert control program is definitely indicated, for active cases appear with disturbing frequency, as will be shown later.

For the past twenty years the 93 units or divisions of the General Motors Corporation have followed a general health program based on three premises:

- 1: "Good housekeeping."
- 2: Control of tuberculosis carriers.
- 3: Educational program.

"*Good housekeeping.*" While this term is usually applied to the orderly arrangement of materials with the view to minimizing occupational accidents, in a larger sense it applies to working conditions as a whole—the control of exposure to toxic compounds, ventilation and, in general, any occupational factor which will adversely affect the workers' health. In 1941 a symposium (5) was held at Saranac Lake, New York under the chairmanship of the late Dr. Leroy U. Gardner to inquire into the various industrial factors affecting the course of tuberculosis. These papers were published, and the opinion was that silica alone

<sup>1</sup> Presented before the Medical Section, as part of the symposium on *Pulmonary Diseases in Industry*, at the 43rd annual meeting of the National Tuberculosis Association, San Francisco, California, June 19, 1947.

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encouraged the progression of tuberculosis. Although other dusts might cause violent reaction in lung tissue, they had little, if any, bearing on the accentuation of preëxisting tuberculous lesions, though they might, and frequently did, affect the worker's general health. The belief in a specific etiological relationship between pulmonary irritation and tuberculosis is so firmly imbedded in the mind of the public, however, that even the medical profession finds it hard to reject, and it thus becomes of considerable medico-legal significance.

In industry, about 2 per cent of all employes have tuberculous pulmonary lesions of some sort, as demonstrated by preëmployment radiographic films. The lesions may be arrested; the greater number of them are, although they exist as potentially active cases in the future. "Good housekeeping" must then concern itself with safeguarding these individuals as well as maintaining the industrial health of the others on a sufficiently high plane to enable them to overcome infection from other sources. Certain types of work produce finely integrated particles of organic or inorganic material which may affect the operator's general health. Buffing, polishing, grinding, sandblasting and paint spraying are in this category. As stated before, it is questionable whether any of these materials, with the exception of silica, has any direct bearing on the reactivation of arrested lesions although they may lead to varying degrees of fibrosis over a period of time. To attempt to protect the worker by means of respirators, masks and the like is a futile gesture, as they are very uncomfortable things to work in and the operator resents working in an environment in which their use is indicated. It is far more simple, and in the end more practical, to keep the dust away from the worker by either eliminating the dust factor or designing exhaust adjuncts which remove it on the spot.

*Control of tuberculosis carriers:* The control of carriers is accomplished in two ways: (1) preëmployment chest films, (2) periodic rechecks.

In each of the divisions of General Motors, some form of preëmployment screening is done. In some, reliance is placed on fluoroscopic inspection but, in the greater number, roentgenograms, either miniature or the standard 14 x 17 size, are used. While fluoroscopy is relatively inexpensive, it has two objections: first, there is no permanent record of findings, merely the transcribed written impressions of the observer; and, second, the factor of error, which in one survey represented 13 per cent in 2,603 examinations (3). Sawyer of Eastman Kodak reports the practice of taking stereoscopic films of each applicant for employment. It is the practice in the Delco Remy Division of General Motors to take 14 x 17 flat films, followed by stereoscopic films in questionable cases. When a person's opportunity to work depends on the interpretation of a roentgenogram, the responsibility thus incurred should not be considered lightly. Where chest films are taken as a prerequisite for industrial employment, individuals whose films show some departure from normal must not be rejected arbitrarily. A policy of that sort is not only an injustice to innocent persons, but defeats its own purpose. Whenever an applicant for employment shows questionable findings, he or she should be referred to a private physician for further study which should include sputum examinations, gastric washings, temperature observations and the like.



In general, only about 10 per cent, or less, of those with questionable findings on the chest roentgenogram will show enough activity to justify concern. The installation of radiographic equipment and the examination of the films by a licensed physician does not assure accurate interpretation by any means. Hilleboe (4) points out that, with the increasing popularity of mass chest surveys, many people who have shown roentgenographic lesions characteristic of early tuberculosis have been arbitrarily labeled as tuberculous in spite of the fact that all other findings were negative. This policy not only does untold harm to both the persons concerned and to the tuberculosis control program, but is scientifically unsound.

To the skilled observer, some chest films show an obviously active condition. On the other hand, one encounters many films which show varying degrees of departure from normal, and the disposition of these cases is the problem with which the industrial observer is confronted. In a mass survey of 936,000 examinations, fewer than 12,000, or 1.2 per cent, showed significant reinfection tuberculosis (6). Allison (8) found a 2 per cent incidence of minimal lesions in preemployment films in another industry. In one division of General Motors, prior to the war (1942) the average incidence of minimal lesions was 1.8 per cent (1). During the war the incidence rose to 4.2 per cent and since then has dropped to 0.8 per cent (1). Neither of the two last values is representative for the reason that the war-time percentage of 4.2 per cent represents experience when Army rejects, submarginal groups and older men and women were employed. The post-war estimate of 0.8 per cent is low for the reason that it includes some 8,000 veterans. Most of this group had had normal chest films in the recent past; otherwise they would not have been accepted for active service. In this connection, of 6,500 former employees who returned to us from military service, 5 had active tuberculosis. Of these, 3 had had minimal apical lesions at the time of employment, *i.e.* prior to entering service, and 2 had had essentially negative chest films. All 5 were referred to the Veterans Administration.

The value of periodic rechecking of all employees cannot be overstressed. While the majority of active cases develop in those who showed minimal lesions on the initial preemployment film, a considerable number occur in persons whose initial film was entirely normal. Age is no criterion. The popular belief that only young people break down is not reflected in our own experience. In the division of General Motors previously cited during the past fifteen years, 36, or 25 per cent of the total active cases, were in persons of 50 or over, and 2 were in their late 60's. Length of service is also relatively unimportant, as will be discussed later. The experience in this same division, which has an annual average employment of 12,000, may be seen in table 1.

The average age of the men at time of employment was 34 years; that of the women, 24. The men worked an average of 6.7 years before becoming disabled; the women, 3.6 years. The longest employment period prior to disability was seventeen years in men and eleven years in women. The shortest was: male, fourteen months; female, eight months. The average age level for both men and women was higher than that reported in 1941, at which time the average for the

men over a ten-year period was 27, rather than 34; the women 20, as compared with 26. This can be explained on the basis that both older men and older women were employed during the war. Of the 51 male cases developing in the past seven-year period, 14, or 27.5 per cent, and of the 25 female cases, 9, or 28 per cent, were employed during that period. Eighty-two per cent of the men and 70 per cent of the women had minimal lesions at the time of employment, as disclosed by their preemployment chest films. All but one of the men over 40 had minimal lesions at time of employment. The women all showed minimal lesions, mostly apical. This would bear out the observation of Allison that, while the general opinion is that apical lesions seldom, if ever, become active, apparently inactive lesions in apices and infraclavicular regions have been the starting point in the majority of cases. Most of the men were employees within the draft age and had been rejected at the induction center because of questionable roentgenographic findings, or were new employees who had been rejected as

TABLE 1

*Cases of active tuberculosis among employees (by periodic check films), Delco Remy Division, General Motors\**

	YEAR							TOTAL	AVERAGE
	1940	1941	1942	1943	1944	1945	1946		
Men.....	5	7	8	7	11	9	4	51	7.4
Women...	4	4	4	2	7	2	2	25	3.6

\* Annual average employment of 12,000.

unfit for military service but could be used in industry. In this connection, Pollak (7) reports that, of the 150,000 inductees rejected at induction centers because of abnormal findings on chest roentgenograms, one-half are alleged to have had active tuberculous lesions. No effort appears to have been made to follow up these cases. Some were advised to see their family doctor, while many others were rejected without any comment as to the reason.

The average disability period was twenty months for both men and women. This is four times longer than that reported for men for the ten-year period immediately preceeding the war, and two and one-half times longer than the average period of disability reported for women. Of the 55 male cases, only 3 died and 41 are now back at work. Nine of the 55 men were over draft age, and their average recovery period was nine months. As to the women (25 cases), none died, and all but one are known to have made a reasonable recovery.

In the General Motors Corporation during a six-year period, 1940-1946, with an average of 210,000 hourly-rate employees, there were 1,383 diagnoses of pulmonary tuberculosis for which claims for sick benefits were filed, an average of 198 cases per annum, or 0.9 per thousand (table 3). The data concerning the sick benefits for respiratory diseases, other than tuberculosis, are presented in table 4.

The rise in the number of tuberculosis cases in 1942 to 1945 can be explained on the basis of war employment, when any man able to stand on his feet, re-

ardless of age, was put to work. The breakdown on the part of the women was caused in large measure by the fact that they had assumed war jobs in addition to their domestic obligations, and did not get adequate rest and nourishment.

The data in table 3 are incomplete because information is not available as to age, length of service prior to illness, duration of disability or outcome. The

TABLE 2

*Disability period after the diagnosis of tuberculosis, Delco Remy Division, General Motors*

	YEAR							AVERAGE
	1940	1941	1942	1943	1944	1945	1946	
	mo.	mo.	mo.	mo.	mo.	mo.	mo.	mo.
Men.....	20	20	30	28	24	8	12	20
Women....	18	20	30	20	26	16	10	20

TABLE 3

*Cases of tuberculosis for which insurance benefits were paid. Experience of entire General Motors Corporation for the past seven years*

	YEAR							AVERAGE
	1940	1941	1942	1943	1944	1945	1946	
Men (Thousand)*.....	168.5	182.0	160.5	200.5	204.0	162.0	133.0	177.2
Women (Thousand)*.....	19.5	22.5	20.0	51.5	83.0	58.0	23.3	39.7
Tuberculosis—Men.....	118	127	177	200	224	205	93	163.4
Tuberculosis—Women.....	18	12	20	52	75	46	23	35.1

\* Total annual employment.

TABLE 4

*Respiratory disease exclusive of tuberculosis for which insurance benefits were paid. General Motors Corporation*

	YEAR							AVERAGE
	1940	1941	1942	1943	1944	1945	1946	
Men.....	4,623	5,514	5,120	9,103	8,151	6,464	2,886	5,980
Women....	1,316	1,676	1,440	5,222	6,142	3,967	1,040	2,972

only facts known are that all these people had a preemployment physical examination and all were disabled for thirteen weeks or more.

*Educational program:* Through the activities of the various tuberculosis associations, the public has become quite tuberculosis conscious, and inquires into the cause of any symptoms which might be associated with this disease. In a decentralized industry, such as General Motors, the majority of the divisions are located in comparatively small cities. No educational program can succeed under these circumstances without the coöperation of the physicians of the community. Periodic health examinations by the plant medical staff, where the findings are available to the private physician, go far toward maintaining a

friendly relationship. It is believed that it is the function of industrial medicine to discover or, by referral from private physicians, to assist in diagnosing, tuberculosis early in its course. Moreover it is a proper function of industrial medicine to help in discovering the source of an infection by taking films of the chests of the patient's family or by other means. Beyond that however, assuming that a particular infection is not industrially incurred, the responsibility for its care rests with the private physician and the local tuberculosis association.

With recognition that it is always easier to induce a tuberculosis patient to undergo sanatorium care when the employer carries adequate group insurance coverage, the General Motors Corporation has provided ample benefits for the majority of such cases. This policy materially affects their early rehabilitation.

#### SUMMARY

1. Tuberculosis in industry can be controlled as an integral part of a general health program, although constant vigilance is indicated.
2. Preemployment physical examinations entail a great responsibility, as well as an opportunity for job selection.
3. Coöperation of local physicians and of the local tuberculosis association is essential in any industrial health program.
4. Ample hospitalization provisions are extremely important as a means to the early rehabilitation of tuberculous cases.

#### SUMARIO

##### *La Lucha Antituberculosa en la Gran Industria*

1. Aunque la vigilancia constante es de rigor, puede cohibirse la tuberculosis en la industria como parte integrante de una obra general pro salud.
2. Los exámenes físicos antes de dar empleo entrañan una grave responsabilidad, pero también permiten escoger mejor el oficio adecuado al individuo.
3. En toda obra pro salud en la industria, es indispensable contar con la coöperación de los médicos y de la asociación antituberculosa de la localidad.
4. Amplios medios de hospitalización revisten suma importancia para la rehabilitación temprana de los tuberculosos.

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# POSTTHORACOPLASTY PULMONARY HERNIA<sup>1,2</sup>

## Report of Four Cases

IRVING PINE AND PHILIP MORGENSTERN

### INTRODUCTION

Maurer and Blades define true hernia of the lung as a protrusion of the pleural-covered lung beyond its normal boundaries through an abnormal opening in the thoracic enclosure (1). They add that some of the earlier case reports were inaccurate because evisceration and prolapse were confused with true hernia. According to Lilienthal (2), a prolapse of the lung occurs when the lung protrudes through an opening to the external world, and would be distinguished from a hernia by the fact that the lung is not covered by any of the thoracic parietes. The comparative rarity of hernia following penetrating wounds of the chest is due to the inherent elasticity of the lungs and the concomitant pneumothorax or hemothorax in the majority of instances.

In the cases here presented, a true hernia existed because in each instance a protruding mass was noted beyond the normal thoracic enclosure. It was covered by thoracic parietes and showed an increase in size on cough and forced expiration with a closed glottis (Valsalva maneuver.)

Extrapleural paravertebral thoracoplasty has rarely been complicated by lung hernia, especially in recent years. Although the operation is the most common type of major surgery performed in the treatment of pulmonary tuberculosis, and the possibility of lung hernia is mentioned in some textbooks of chest surgery, no instances of its occurrence have been described in the American literature (1, 3, 4, 5). It has been stated that, when the periosteum and intercostal muscles are left intact, complications like lung hernia do not occur (6). Brauer's suggestion was to avoid resecting the periosteum with the ribs, so that regeneration could occur and result in fixation of the chest wall with new bone (7).

The present report deals with 4 cases of lung hernia which followed thoracoplasty. Although there were individual differences in each of the cases, there were also certain common factors which help to identify this unusual complication.

### CASE REPORTS

*Case 1:* The patient, N. M. G., is a 53-year-old white female with a tuberculous cavity in the right upper lobe which was demonstrated roentgenographically in July, 1942. An attempt at pneumothorax was unsuccessful. Two stages of thoracoplasty were performed in March and April, 1943, with removal of posterior segments of the upper six ribs. Ten per cent formalin was applied locally to the rib beds at the time of each operation. Fol-

<sup>1</sup> From the Department of Medicine and Surgery, Veterans Administration, Oteen, North Carolina.

<sup>2</sup> Published with permission of the Chief Medical Officer, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

lowing the second stage of thoracoplasty, the patient complained of pain and extreme sensitivity over the operative scar. These symptoms persisted and did not respond to analgesics or to the local injection of novocaine.

A third-stage thoracoplasty was performed July 10, 1944. A 4 by 6 cm. oval area lateral to the fourth, fifth and sixth transverse processes was noted, through which the lung had herniated. (This hernia was not diagnosed preoperatively.) The neck of the seventh rib, the distal end of the transverse process, and 12 cm. of the seventh rib were removed. The seventh intercostal nerve was crushed just lateral to the transverse process and the hernia was repaired by freeing the contents and sewing together the cleavage planes.

After operation the pain became worse and was indistinguishable from causalgia. The patient preferred to sleep hunched up in a jackknife position on her normal side and complained bitterly of the pain in the intercostal spaces. An area of hyperesthesia 5 by 6 cm. was present in the right interscapular area. The pain in the interspaces was not easily defined. The patient described it as "pinching, burning, aggravated by being up and about." She was unable to withstand the slightest touch over the thoracoplasty scar.

The pain persisted and was not controlled by the daily administration of 6 grains of codeine. Several intercostal nerve blocks and neurectomy also failed to give any relief. It was believed that the pain was causalgic in nature. The patient was gradually given diminishing doses of codeine and continual assurances that the pain would eventually subside. She was discharged in March, 1947, as an arrested case, having adjusted to the pain so that she could now get along without codeine.

*Comment:* The diagnosis of lung hernia was made at operation. The roentgenographic and physical findings had not disclosed this condition. The severe prolonged causalgic type of pain was so unusual, however, that it might have suggested the diagnosis. The treatment with neurectomies and nerve blocks seems to have been of dubious value. Sympathetic block, followed later by sympathectomy, would have been the treatment of choice in the early stages of the painful syndrome.

It is interesting to note that, although the repair of the lung hernia was successful, the causalgic pain continued.

*Case 2:* T. R., a 51-year-old male, was first discovered to have tuberculosis in 1925. From September through December, 1940, he had a seven-rib thoracoplasty for a cavitary lesion of the right upper lobe. Ten per cent formalin was applied locally to the rib bed at the time of each operation.

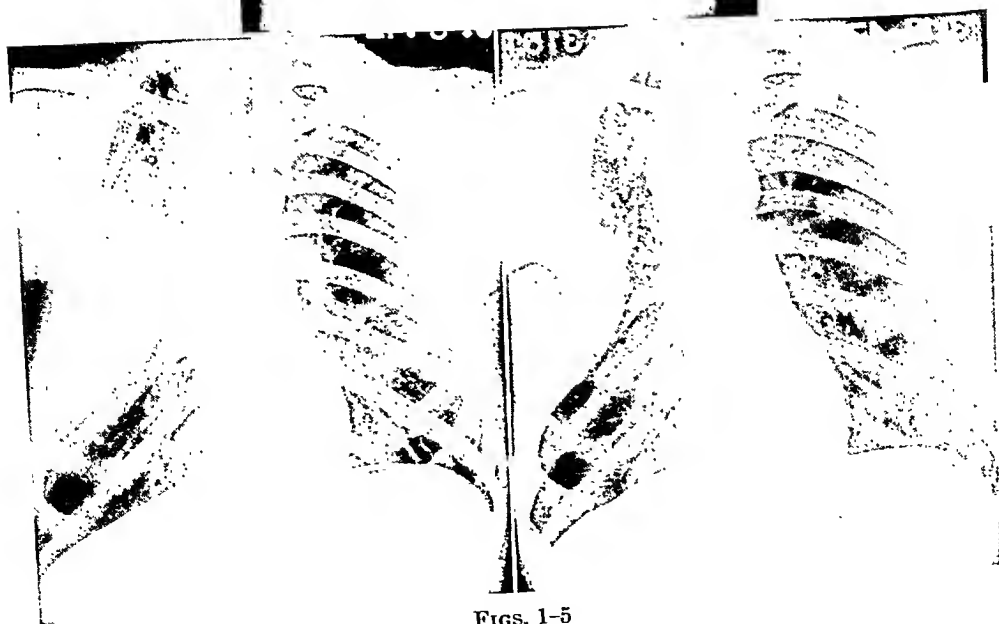
Following the last stage of thoracoplasty, the patient developed moderate pain in the region of the right scapula. This became worse after his discharge from the hospital in 1941, and he was soon receiving as much as five doses of pantopon daily from a private physician.

In May, 1946, the patient returned to the hospital. He described the pain as "cutting, burning, like a hot furnace." "The only time the pain was better was when I didn't walk and somehow became completely relaxed."

Physical examination revealed a small, bulging mass, about 3 by 5 cm. in diameter, in the thoracoplasty scar at the inferior end of the scapula. The mass became larger on cough, forced expiration and with the Valsalva maneuver. Roentgenogram of the chest revealed a well-defined lung hernia (figure 1).

A plastic rib repair of the lung hernia was attempted. The size of the hernia was reduced following operation (figure 2), but the pain persisted.

In August, 1946, five separate attempts at nerve block with alcohol and novocaine were



FIGS. 1-5

followed by no relief. Thoracic sympathetic block was attempted in September, 1946, and resulted in relief of pain for about one-half hour.

A resection of the fifth and sixth intercostal nerves under a general anesthetic was performed on October 16, 1946. No relief ensued and the patient was discharged on November 7, 1946, as having obtained maximum hospital benefit. For two months before discharge he received only salicylates and barbiturates for control of pain.

The patient returned to his private physician, from whom he obtained codeine and pantopon as previously, but the severe pain made him return to the hospital February 12, 1947. One month later he had another nerve resection (sixth intercostal nerve), which failed to give relief. The patient insisted on receiving codeine. He attempted suicide April 21, 1947, by slashing his external jugular veins with a razor.

*Comment:* Lung hernia was diagnosed from the physical findings and the chest roentgenogram. Repair was unsuccessful, possibly due to the long-standing (six years) nature of the defect. The pain, which was variously diagnosed as drug addiction, malingering, and psychoneurosis, was not relieved by nerve section or injection. The difficulty in this case is that the causalgic syndrome has been present for so long that a sympathetomy would probably not now be successful.

*Case 5:* J. T. R., a 53-year-old male, was found to have tuberculosis in December, 1943. In July, August and September, 1946, a three-stage thoracoplasty was performed for a fibrocaseous lesion of the left upper lobe. After the first stage the patient complained of persistent pain in the left axilla. He continued to complain of pain in the left arm and shoulder for the next five months and he also noted numbness and tingling sensations in the left hand and arm. Symptoms were worse when the patient lay on the affected side and when he was up and about for a period of time. At present (August, 1947) the pain is not so troublesome as it was six months ago, but a dull ache in the left axilla is present almost continuously. Herniation of the lung in the upper axillary portion of the left chest may be seen in the roentgenogram (figure 3).

*Comment:* Numbness and tingling in the upper extremity on the affected side were prominent features and may have been caused by pressure from the hernia on the brachial plexus. On the whole, the pain in this man was milder than in the 2 preceding cases and the patient gradually adjusted to it.

*Case 4:* F. M. is a 39-year-old male who had a cavitary lesion of the right upper lobe. Three stages of posterior thoracoplasty were performed in May, June and July, 1942, with removal of segments of the upper seven ribs. Ten per cent formalin was applied to the posterior sections of the rib beds after each stage. An anterior stage was done in August, 1942, with removal of the anterior stumps of the fourth and fifth ribs and the cartilages of the upper four ribs.

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FIG. 1. (Upper left) Case 2. Chest film May 29, 1946. Large hernia is seen in right axilla at lower border of the scapula.

FIG. 2. (Upper right) Case 2. April 21, 1947. Hernia is reduced in size after plastic repair, but is not completely obliterated. Transplanted rib is held in place by silver wire.

FIG. 3. (Centre) Case 3. March 25, 1947. Diffuse herniation of the lung in the left upper chest.

FIG. 4. (Lower left) Case 4. September 8, 1942. Showing diffuse herniation of the lung in the right upper axilla shortly after thoracoplasty.

FIG. 5. (Lower right) Case 4. March 18, 1947. Chest film four and one-half years later. No attempt was made to repair this hernia.



Review of the chest film after the second stage revealed that there was already present at that time the radiolucent bulge in the right upper axilla, which is now identified as characteristic of lung herniation (figure 4).

The patient had frequent hard coughing spells after the third-stage operation. He complained of dull chest pain and occasional dyspnea.

On October 27, 1943, a revision operation was performed because of a persistent draining sinus at the lower angle of the operative scar. In a second revision operation on December 1, 1943, regenerated portions of the second, third, fourth and fifth ribs were resected. "A substantial increase in degree of collapse of the lung" was obtained. His sputum became negative for tubercle bacilli in April, 1944, and has remained so to date. In 1946, the patient was readmitted to the hospital because of an acute upper respiratory infection. At that time he was found to have a large mass beneath the right scapula. The possibility of a tuberculous abscess was considered as he was known to have had previous tuberculous involvement of the lumbar spine. However, closer observation of the character and changing size of the bulge on cough and forced expiration led to the correct diagnosis. Roentgenography revealed a large herniation of the right upper lung into the axilla (figure 5). The patient apparently had no symptoms at this time except for a slight tugging sensation in the right shoulder and upper chest when he coughed.

*Comment:* No attempt was made to repair the hernia in this case as the patient's symptoms were not too troublesome. Moreover, it is doubtful whether surgery would be successful in obliterating a chest wall defect of such size.

#### DISCUSSION

Montgomery and Lutz (3), in discussing the symptomatology of lung hernia, state: "Pain and distress are always present." There is "insidious onset, pain in the region of the hernia, a pulsion mass and usually a chronic cough which ejects the lung at intervals making the patient twinge with pain as if he had pleurisy."

All 4 patients of the present study had pain in the shoulder or axilla of the operated side which usually appeared after the second or third stage of thoracoplasty. In 2 patients the pain was so intense that it was indistinguishable from the pain described in causalgia. The other 2 patients had pain of a milder nature, usually made worse by lying on the affected side or being up and about for long periods of time. Pain of such a character, which appears after thoracoplasty, should direct the examiner's attention to the possibility of pulmonary hernia. One patient complained frequently of numbness and tingling in the upper extremity on the affected side. Frequent hard coughing spells were a prominent symptom in one case, but were not present in the other 3 patients.

In case 4, the mass at first suggested a cold abscess produced by tuberculous involvement of either the spine or a rib. A pulmonary hernia may also simulate an empyema necessitatis or a tumor. The bulging mass may protrude beyond the normal confines of the chest so that the lung hernia is easily identified. It is important to remember, however, that the hernia may be completely or partially obscured by the scapula or the heavy musculature of the latissimus dorsi or the anterior pectoral muscles. What seems to be a small bulge on the chest wall may appear as a huge hernia on the film. The bulging mass should also be

checked by careful palpation during cough and in forced expiration with a closed glottis. Vague crepitation was an occasional finding in the cases described and the mass was rather soft and fluctuant like an air cushion. In none of the cases was there any definite tenderness over the mass.

In 3 of the cases definite roentgenologic evidence of pulmonary hernia was noted. An area of increased illumination was seen protruding beyond the normal confines of the thoracic cage and accompanied by incomplete or defective regeneration of the ribs. Normal lung markings could be identified, which helped to differentiate the hernias from lung cyst, cavitation or bleb formation. The area of increased radiolucence appeared either as a convex shadow in the upper portion of the chest continuous with the rest of the pulmonary tissue, or as a sac-like structure outside of the bony cage and connected with the rest of the lung by a small isthmus.

In case 4 no attempt was made to correct the defect because of the possibility of causing more pain after repair of the hernia. Although many successful repairs of traumatic hernias have been reported where the lung protruded through a small defect between two ribs, it is quite another matter to replace successfully a herniated lung where a large portion of the thoracic cage is absent.

From recent experience with causalgic states, it would seem that sympathetic block or resection is the treatment of choice where the pain is of the characteristic severe burning type. As regards the cause of lung hernia, destruction of the rib bed by formalin and consequent defective restoration of thoracic parietes were probably factors in cases 1, 2 and 4.

An unusual amount of persistent cough between stages of thoracoplasty, before the ribs have had a chance to regenerate, may be a factor in the etiology. This would be in line with the concept that most hernias in adults are caused by a frequently repeated strain over a period of time.

#### SUMMARY

1. Four instances of postthoracoplasty pulmonary hernia are reported.
2. The roentgenographic findings, physical signs and symptoms are described and the possible causes of this condition are discussed.
3. Pulmonary hernia should be considered in the differential diagnosis of any postthoracoplasty patient in whom persistent intercostal pain or pain in the shoulder or axilla occurs, together with a pulsion mass on the chest wall.

#### SUMARIO

##### *Hernia Pulmonar Posttoracoplástica: 4 Observaciones*

1. Descríbense 4 casos de hernia pulmonar posttoracoplástica.
2. Discútense los hallazgos roentgenológicos, y los síntomas y signos físicos, sugiriéndose posibles causas de dicho estado.
3. Debe considerarse la hernia pulmonar en el diagnóstico diferencial de todo caso posttoracoplástico en el que haya persistente dolor intercostal o en el hombro o axila junto con una tumefacción pulsante en la pared torácica.

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# PARTIAL SCAPULECTOMY<sup>1,2</sup>

## An Anterior Approach

WILSON WEISEL AND MELVIN A. CASSEL

### INTRODUCTION

In the course of thoracoplasty with removal of five to seven ribs, the presence of an intact scapula may cause disability, pain, discomfort and deformity, due to the scapula overriding or impinging on the lower ribs. The intact scapula has also been implicated as a reason for inadequate pulmonary collapse (6). These complications may be corrected by the removal of more ribs or by partial scapulectomy. The latter operation has become an accepted and established procedure in the surgical treatment of some cases of pulmonary tuberculosis during the past ten years (2, 6, 8). The conventional approach for this operation has been through a posterolateral incision at the time of, or following, the last posterior thoracoplasty procedure (3, 4, 5, 6, 7, 9). The writers found it advantageous, however, to use an anterior approach for partial scapulectomy in conjunction with an anterior thoracoplasty in a selected group of patients, and it is for the purpose of describing the technique of the procedure that this paper is presented.

### INDICATIONS FOR THE ANTERIOR APPROACH

The performance of partial scapulectomy through an anterior incision at the time of anterior chondrocostectomy was first employed in a small group of patients in whom the posterior stages with resection of six or seven ribs had been completed, but scapulectomy and anterior thoracoplasty were still indicated. It was believed that, by this procedure, an additional operation of scapulectomy through a posterior approach was made unnecessary. Because of the ease and small risk of the procedure, it was thought to be worth while to continue using it in the following two groups of patients: *a*) poor risk patients in whom it is felt at the time of posterior thoracoplasty that an additional scapulectomy is not indicated because of the increased trauma and operating time involved; *b*) patients in whom the collapse after removal of five to seven posterior ribs was better than anticipated, but who continued to suffer from complications due to an intact scapula. It seemed to the writers that patients tolerate anterior thoracoplasty better than posterior stages and that the postoperative reaction from partial scapulectomy has been similarly less when performed with the anterior stage than when performed with a posterior stage.

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<sup>2</sup> Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

## TECHNIQUE

The following technique has been employed for anterior partial scapulectomy. The patient is placed in the supine position on the operating table with a small pillow under the shoulder of the operative side. The arm of the operative side is abducted 90 degrees and the elbow is flexed about 15 degrees. The arm is held in this position by suspending it by a gauze bandage passed around the well padded wrist and carried over an intravenous standard which is set at the proper height. The anesthesia most commonly employed has been intravenous sodium pentothal with oxygen or cyclopropane.

An anterior axillary oblique incision is used, similar to that described by Haight (5). The incision is made along the lateral border of the pectoralis major muscle extending from the anterior axillary fold to the level of the fifth rib. After

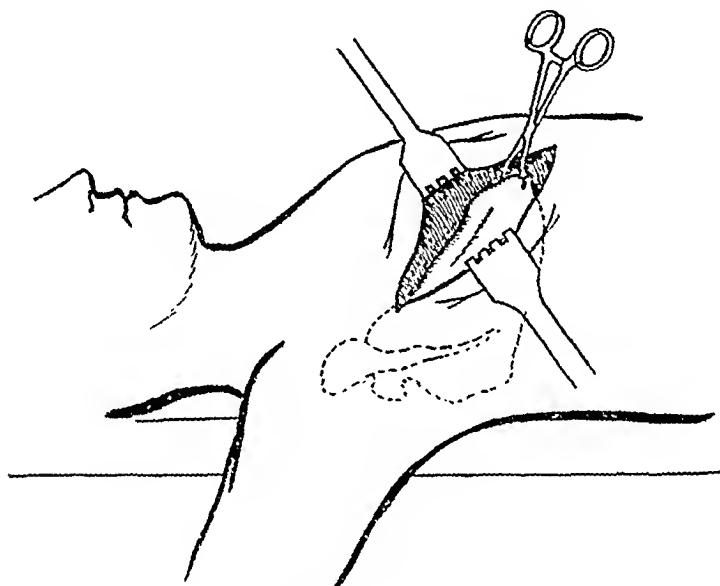


FIG. 1. Diagrammatic drawing showing exposure of scapula in anterior wound

carrying the incision down through the pectoral fascia, the pectoralis major muscle is retracted medially and anteriorly for the anterior thoracoplasty.

Following the anterior thoracoplasty, the latissimus dorsi is retracted laterally and the inferior angle of the scapula is brought up into the wound by means of tension on a towel clip placed in the inferior angle (figure 1). An incision is then made through the subscapularis muscle and periosteum around the edge of the lower one-third of the scapula. The periosteum and subscapularis are separated from the scapula by a sharp periosteal elevator and retracted upward. The serratus anterior tendon is then cut from the inferior angle, and the infraspinatus muscle and dorsal periosteum are separated from the scapula as described above and retracted upward.

The desired amount of scapula is then resected, using a Bethune rib cutter and bone rongeur. Hemostasis is ensured by transfixion ligature of the descending

branches of the transverse scapular and subscapular vessels and any other bleeding point. The subscapularis and infraspinatus muscles are then approximated below the inferior edge of the scapula and these muscles are attached to the anterior serratus where the latter was detached from the resected scapula.

The wound is then closed by suturing the skin. All wounds are drained for twenty-four hours by a Penrose drain placed in the subscapular space and brought out through a stab wound below the original incision. Cotton is routinely used as the suture material.

The operation described above has been performed on 12 patients in this hospital during the past year, of which the following 6 cases are illustrative.

#### CASE REPORTS

*Case 1:* D. L., a 22-year-old white male, was found to have moderately advanced tuberculosis of the left upper lobe in October, 1944, and was treated with left pneumothorax. In February, 1946 he developed a right apical lesion which rapidly progressed to fibrocavitation and cavitation within four months, despite complete bed-rest. A right-sided thoracoplasty was decided upon as the most effective therapy and a two-stage, six-rib thoracoplasty was begun in August, 1946. Following the second stage, the patient developed constant pain in the scapular area with a fixed scapula, marked difficulty in moving his right arm, and an elevated right shoulder. It appeared that collapse of the diseased right lung was satisfactory following the second posterior stage. Therefore, partial scapulectomy was performed at the time of the anterior thoracoplasty in September, 1946. Convalescence following the operation was uneventful and the patient was able to move his right arm and shoulder satisfactorily without pain. In addition, the preoperative scapular pain had disappeared.

*Case 2:* C. W., a 25-year-old colored male, was diagnosed as having minimal right apical tuberculosis in October, 1943. He was treated with bed-rest and gradual resumption of activities and discharged as an arrested infection in September, 1944. In August, 1945 his sputum was found to be positive for tubercle bacilli and a roentgenogram on readmission revealed moderately advanced productive tuberculosis of the right upper lung. Right pneumothorax was attempted but was unsatisfactory and a right thoracoplasty was recommended. In August, 1946 a two-stage, six-rib thoracoplasty was begun and further rib resection was considered unnecessary after the second stage. Partial scapulectomy was then performed at the time of anterior thoracoplasty in October, 1946, because of an elevated right shoulder and inability to move the right arm satisfactorily because of fixation of the scapula. The inferior angle of the scapula had been caught under the seventh rib. Following the partial scapulectomy, the patient was able to move his right arm and shoulder in a satisfactory manner and there was a drop in the height of the right shoulder to a more normal position.

*Case 3:* R. B. S., a 21-year-old colored male, was diagnosed as having moderately advanced tuberculosis of the left upper lung in May, 1945. Left pneumothorax was begun in July, 1945, but was ineffective because of pleural adhesions which did not appear to be amenable to section by pneumonolysis. In December, 1945 a left temporary phreniclasia was performed. A roentgenogram in September, 1946 revealed a cavity in the left infraclavicular area and a thoracoplasty was recommended at this time. Two-stage, six-rib thoracoplasty was begun in December, 1946. After the second stage, it was believed that

effective pulmonary collapse was achievable by anterior thoracoplasty without further rib resection and a partial scapulectomy was performed at the time of anterior thoracoplasty in February, 1947. The partial scapulectomy was performed because the lower angle of the scapula impinged upon and "rode over" the seventh rib, causing pain in the scapular area on movement of the arm. It was also believed that, with excision of the inferior scapula, a better collapse could be obtained. Postoperative convalescence was uneventful and the patient could move his arm without pain after the partial scapulectomy. Collapse of the lung was considered to be satisfactory and complete.

*Case 4:* M. W., a 23-year-old white male, was first hospitalized for pleurisy in 1941, while in military service. He was discharged in one month and returned to duty. In 1943 his chest pain recurred and he was again hospitalized with a diagnosis of active, minimal, exudative tuberculosis. A left pneumothorax was started in January, 1944, because of progression of the lesion. The patient left the hospital against medical advice and neglected to have the pneumothorax maintained. He was readmitted to the hospital in January, 1946, and at this time a moderately advanced lesion was found in the apex of the right lung and his sputum contained tubercle bacilli. In January, 1946 a right pneumothorax was started, but it was abandoned because of unsatisfactory collapse. A right temporary phreniclasia was performed in June, 1946, and repeated in July, 1946, but a complete diaphragmatic paralysis was not obtained. In February, 1947 a right two-stage, six-rib thoracoplasty was begun and it was felt that adequate pulmonary collapse could be obtained with anterior thoracoplasty following the second stage. The patient had marked scapular pain on movement of the right arm, a fixed scapula and an elevated right shoulder. Consequently, at the time of anterior thoracoplasty in April, 1947, a partial scapulectomy was performed. Following operation, the patient had a gradual return of normal, painless movement of the right arm and shoulder.

*Case 5:* R. F., a 23-year-old white male, was found to have tuberculosis in June, 1945. At the time of his initial diagnosis, he had a moderately advanced, exudative lesion with cavitation in the left upper lobe. In August, 1945 left pneumothorax was begun and a left pneumonolysis was performed in October, 1945. The patient was admitted to this hospital in March, 1946, where the pneumothorax was abandoned as inadequate. In November, 1946 planigrams of the left upper chest, following reexpansion of the pneumothorax, revealed cavitation and thoracoplasty was advised. A two-stage, six-rib thoracoplasty was begun in January, 1947. The second stage operation was limited to the removal of three ribs because the patient developed a marked drop in blood pressure, a rapid, thready pulse and respiratory difficulties. Following the second stage, it was felt that pulmonary collapse would be adequate after anterior thoracoplasty. This patient had a fixed scapula and marked elevation of the left shoulder following his second stage. In February, 1947 partial scapulectomy was performed at the time of an anterior thoracoplasty. Convalescence was uneventful, the patient regained his scapular motion and noted a gradual return of the left shoulder to a lower and more normal position.

*Case 6:* V. J. G., a white male patient, age 27 years, was diagnosed as having right minimal apical tuberculosis while in military service in February, 1944. A right pneumothorax was induced in April, 1944. While in transit to a different hospital the pneumothorax was inadvertently abandoned and attempts to reinduce it in June, 1944 were unsuccessful. In August, 1944 a right phreniclasia was performed. The right phrenic nerve was re-crushed in August, 1946 and, despite sanatorium care, the patient continued to expectorate

tubercle bacilli and his disease progressed to a moderately advanced right apical, fibrocavitary lesion. Consequently, a right thoracoplasty was begun in May, 1947. Following a two-stage thoracoplasty with removal of six ribs, it was believed that the pulmonary collapse would be adequate after an anterior thoracoplasty. Following the second-stage thoracoplasty, however, the patient had pain on movement of the right upper arm resulting from overriding and rubbing of the lower angle of the scapula on the seventh rib. In July, 1947 the patient had an anterior thoracoplasty with partial scapulectomy from the anterior approach. Following this operation, the patient has done well. His sputum has been negative and he has been able to move his right arm and shoulder without pain.

#### ADDITIONAL CASES

The operation herein described was performed on 6 additional patients, although the results are not being reported in detail. The partial scapulectomy was performed in each instance in an attempt to correct scapular pain on movement of the shoulder and arm and elevation of the shoulder resulting from an overriding scapula in which the lower angle impinged on, or rode over, the seventh rib. The operation was performed at the time of anterior thoracoplasty in one instance because the patient's condition did not permit further surgery at the time of the posterior thoracoplasty. In the 5 remaining cases, scapulectomy was performed with anterior thoracoplasty because further posterior rib resection was not deemed necessary after the second posterior stage.

#### SUMMARY

An anterior approach for partial scapulectomy in conjunction with an anterior thoracoplasty is presented. Twelve patients have been operated upon during the past year, using the technique described. The course of 6 of these patients is presented in detail in order to illustrate the type of case in which the operation has been used.

#### SUMARIO

##### *Escapulectomía Parcial: Vía de Acceso Anterior*

Expónese una vía de acceso anterior para la escapulectomía parcial en conjunción con una toracoplastia anterior. Con la técnica descrita se ha operado a 12 tuberculosos durante el año pasado. A seis de estos enfermos se les presenta como típicos de los casos en los que se ha empleado esta intervención.

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# STREPTOMYCIN AND THOROCOPLASTY<sup>1</sup>

## Two Cases Treated with Streptomycin for Contralateral Disease

M. MAXIM STEINBACH, GEORGE C. LEINER, ABRAHAM A. POLACHEK AND PAUL HELLER

Indications for, and contraindications to, thoracoplasty are well established. Active tuberculosis in the contralateral lung is considered to be a contraindication to thoracoplasty. It is advisable to postpone the operation until the disease in the other lung is stabilized. To achieve this, collapse of the "better" lung by pneumothorax is sometimes necessary. Many thoracoplasties have to be deferred indefinitely because of progressive disease in the contralateral lung.

Active tuberculosis may become arrested or absorbed following streptomycin administration. It seems, therefore, that patients who are unsuitable for thoracoplasty because of progressive disease in the contralateral lung could be made suitable by streptomycin treatment. Hinshaw and coworkers (1) say: "Other patients with inoperable pulmonary tuberculosis have apparently improved sufficiently to undergo such operations as thoracoplasty and pulmonary resection."

In a somewhat different indication, Hinshaw and coworkers (2) and Glover *et al.* (3) used streptomycin before and after thoracic surgery. They believe that streptomycin, given preoperatively and postoperatively, may prevent a post-operative spread of the disease in patients who undergo thoracoplasty or lung resection for pulmonary tuberculosis.

The present report is concerned with 2 patients with pulmonary tuberculosis who had been unsuitable for thoracoplasty because of contralateral disease, in whom streptomycin treatment caused such improvement that a successful thoracoplasty could be performed.

### CASE REPORTS

*Case 1:* P. N. The patient was a 28-year-old colored female, whose disease started in October, 1944, with fatigue, loss of weight, chest pain and cough. A chest roentgenogram revealed pulmonary tuberculosis and in December, 1944 the sputum was positive for tubercle bacilli on direct smear. The patient rested at home and was eventually admitted to Montefiore Hospital on April 6, 1945. On admission (figure 1A), tuberculous pneumonia, involving the major part of the left lung, was found and the sputum was positive for tubercle bacilli on direct examination. An occasional wheeze was heard over the chest, but bronchoscopy in April, 1945 was negative except for some redness of the left main bronchus. A left pneumothorax was induced on April 23, 1945, and a partial pneumonolysis was done on August 13, 1945. Thoracoscopy on October 11, 1945 revealed the pleura to be markedly inflamed. The left pneumothorax was discontinued on August 26, 1946 as technically unsatisfactory and clinically ineffective. A pleural effusion developed and repeated taps yielded turbid fluid which revealed no tubercle bacilli on smear or culture. In October, 1946, when the left lung had reexpanded only slightly, a spread of the disease developed in the right upper lobe. This exudative process showed rapid

<sup>1</sup> From the Division of Pulmonary Diseases, Montefiore Hospital, New York, New York.

progression and the sputum, which for some time had been positive on concentrate only, became positive on direct smear. The chest roentgenogram taken on December 12, 1946 may be seen in figure 1B. Streptomycin treatment was started on December 19, 1946, and continued until May 8, 1947. The patient received 2.0 g. of streptomycin daily, intramuscularly, in doses of 250 mg. every three hours. The exudative lesions in the right upper lobe showed marked resolution on successive roentgenograms to the point of almost complete disappearance. An eight-rib thoracoplasty on the left was performed in three stages on March 23, April 14 and May 5, 1947. The residual minimal lesions in the right upper lobe have remained stable since March 13, 1947 (figure 1C). Sputum and gastric cultures have been negative. The patient is in excellent general condition (June, 1948). She was discharged in December, 1947, with arrested pulmonary tuberculosis. At no time were there any side effects from the streptomycin.

*Case 2: S. H.* The patient was an 18-year-old white male. The onset of his disease was in December, 1945, with a tuberculous pneumonia of the right upper lobe. The patient was admitted to Montefiore Hospital on March 2, 1946. The sputum was found positive for tubercle bacilli on smear. A right pneumothorax was induced on March 9, 1946. A partial pneumonolysis was done on May 31, 1946. Thoracoscopy on July 16, 1946 revealed extensive adhesions which were not considered suitable for division. The right phrenic nerve was crushed on July 29, 1946. A pleural effusion developed, which was amber, thin and revealed no tubercle bacilli on direct examination. Pneumothorax was discontinued on September 30, 1946. A spread of the disease to the left lung appeared in November, 1946, and progressed slowly. The chest roentgenogram taken on January 31, 1947 may be seen in figure 2A. Streptomycin treatment was started on this day. The sputum revealed tubercle bacilli on direct smear. The patient received 2.0 g. of streptomycin daily, intramuscularly, in doses of 250 mg. every three hours, until June 1, 1947. From June 1 to June 20, the patient received 1.0 g. of streptomycin daily, intramuscularly, in doses of 166 mg. every four hours. Roentgenograms disclosed steady slow resorption of the lesions in the left lung (figure 2B). An eight-rib thoracoplasty on the right was performed in three stages on April 28, May 19 and June 5, 1947. The lesions in the left

FIG. 1. Chest roentgenograms of case 1, P. N.

A. (Upper left) April 9, 1945. Left lung—tuberculous pneumonia involving the major part of the lung. Right lung—normal. Heart and mediastinum displaced to the left.

B. (Upper right) December 12, 1946, before streptomycin treatment was started. The left lung is partially collapsed by pneumothorax and there is a small amount of pleural effusion. In the right lung may be seen soft confluent infiltrations between the clavicle and the second anterior intercostal space.

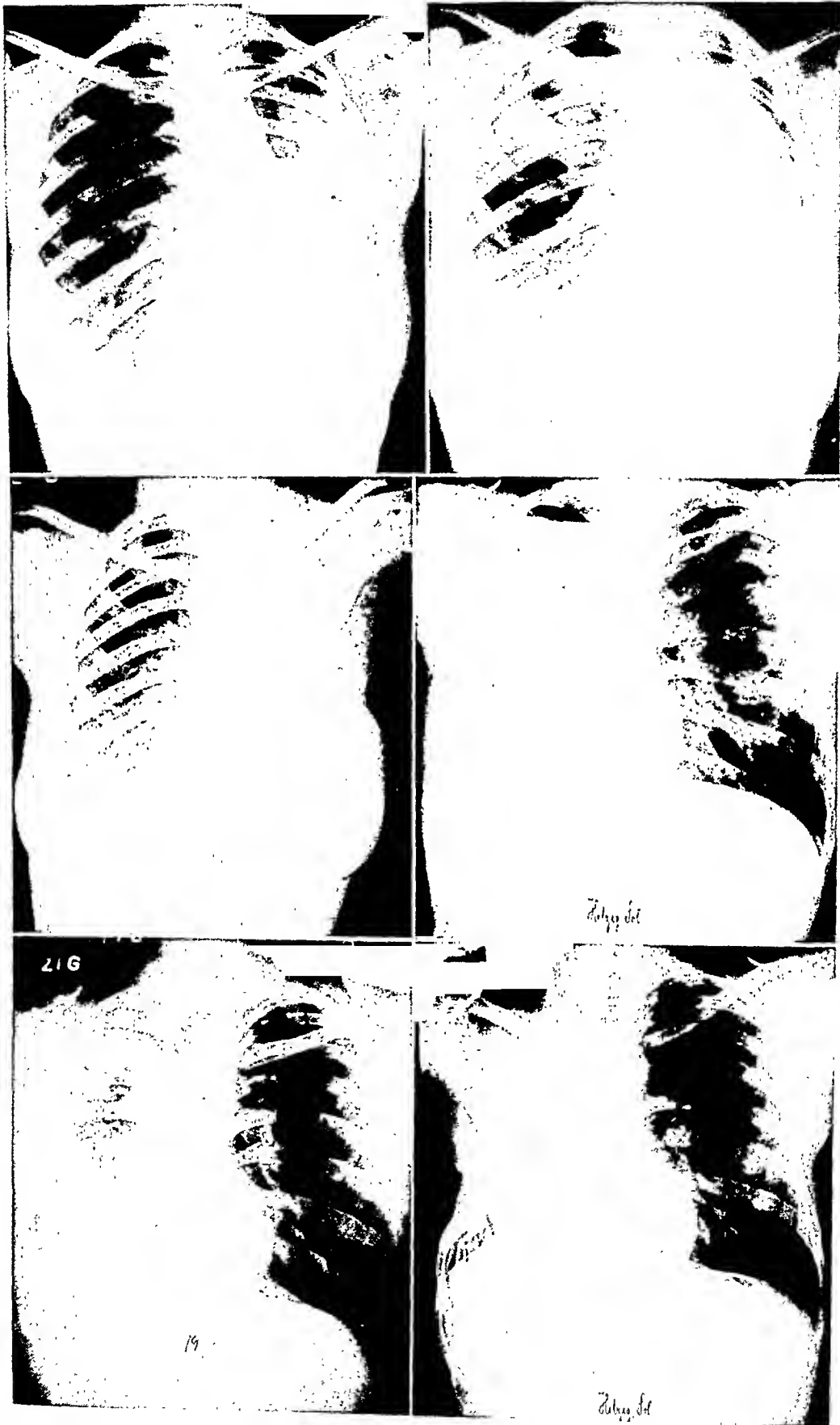
C. (Centre left) May 15, 1947, after streptomycin treatment. The left lung is collapsed by an eight-rib thoracoplasty. Right lung—in the first and second anterior intercostal space there are a few linear shadows.

FIG. 2. Chest roentgenogram of case 2, S. H.

A. (Centre right) January 31, 1947, before streptomycin treatment was started. The right lung is partially collapsed by a hydropneumothorax with a fluid level above the clavicle. Left lung—confluent nodular shadows between the apex and the fifth anterior rib. Trachea, heart and mediastinum are displaced to the right.

B. (Lower left) April 28, 1947, after three months' streptomycin treatment. Right lung—there has been some reexpansion of the lung; the air and most of the fluid have been absorbed. Left lung—there has been considerable regression and hardening of the lesions.

C. (Lower right) July 25, 1947. The right lung is collapsed by an eight-rib thoracoplasty. Left lung—lesions have remained stable.



FIGS. 1A to 2C

upper lobe remained stable, sputum and gastric cultures became negative for tubercle bacilli. Toxic effects of the streptomycin treatment were: a slight paresthesia around the mouth, which appeared three days after the start of the treatment and which lasted a few days; dizziness, which developed in the fifth week of treatment. The dizziness began to improve in the eighth week of treatment and disappeared nearly completely. The patient is in excellent general condition (June, 1948). He is ambulant.

#### DISCUSSION

The 2 patients described above show some similarities in the development of their disease. In both, the disease started with an extensive caseous pneumonia. Pneumothorax was induced in both patients, but had to be discontinued after several months because of adhesions and because of the development of pleural effusion. During the slow reëxpansion of the lungs prior to thoracoplasty, new exudative lesions appeared in the contralateral, previously normal lungs. The new lesions showed continuous progression. In the presence of active contralateral lesions, both patients were unsuitable for thoracoplasty. Consequently, the prognosis appeared very poor in both patients, one of whom was a young Negro girl. After progression of the disease had been observed in both patients for more than two months, streptomycin treatment was started. Two g. were given daily, intramuscularly in doses of 250 mg. every three hours. The first patient was treated on this regimen for almost five months. The second patient received the 2.0 g. daily dose for four months, and then 1.0 g. daily during the ensuing three weeks. The reduction in dose was made because of a shortage of the drug. After the institution of chemotherapy, dramatic improvement took place in both patients. After three months of treatment, when the lesions had nearly completely resorbed and appeared stable, three-stage thoracoplasties were performed. No evidence of progression of the disease appeared following the operations. Both patients recovered rapidly from the operations and are now in excellent general condition. The contralateral lesions have remained stable until the present time and cultures of sputum and gastric washings have become negative for tubercle bacilli. No toxic effects from streptomycin were observed in the first patient. The second patient complained of short-lasting paresthesia around the mouth and of dizziness, which improved subjectively during and after the streptomycin treatment. There were no other complications. Routine studies of the blood and urine revealed no abnormalities.

Without streptomycin treatment, in all probability, both patients would have continued their downward course. In both instances thoracoplasty was definitely contraindicated when the disease was active and progressive in the contralateral lung. Under streptomycin treatment the lesions regressed and remained stable. Both patients improved to such a degree that successful thoracoplasties could be performed. From these observations, it is to be hoped that streptomycin will help to make suitable for thoracoplasty or other forms of chest surgery many patients who, without streptomycin, would continue a downhill course.

#### SUMMARY

Two patients are presented in each of whom an ineffective pneumothorax had to be abandoned. While waiting for reëxpansion of the lungs, progressive tuber-

culous disease in the contralateral lungs developed. In both instances, the disease in the contralateral lung improved to such a degree under streptomycin therapy that it was possible to perform a successful thoracoplasty on the originally affected side.

#### SUMARIO

##### *Estreptomicina y Toracoplastia: Dos Casos Tratados con Estreptomicina por Afcción Contralateral*

Preséntanse dos enfermos, en ambos de los cuales hubo que abandonar un neumotórax infez. Mientras esperaban la reexpansión de los pulmones, manifestaron enfermedad tuberculosa evolutiva en el pulmón contralateral. Con la estreptomycinoterapia la enfermedad contralateral mejoró a tal punto que pudieron ejecutarse toracoplastias con éxito en el lado afectado primitivamente.

#### *Addendum*

Since this article was written, a third similar case, treated successfully with streptomycin and thoracoplasty, has been observed by the writers.

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# PLEURISY WITH EFFUSION DURING PNEUMOTHORAX THERAPY<sup>1</sup>

Etiology, Bacteriology, Complications and End Results

JOHN B. MORRISON<sup>2</sup>

The problem of the etiology of pleural effusions occurring during artificial pneumothorax therapy has exercised the minds of many workers in sanatoria. A considerable diversity of opinion is found on examining the literature relating to this subject, and it seemed to the writer that a comprehensive clinical and laboratory study of an adequate number of patients would be of value, not only in elucidating the causes of such effusions, but also in guiding the physician in his selection of patients for pneumothorax therapy and his conduct of their treatment.

There is considerable variation in the figures given by workers in this field in relation to the demonstration of tubercle bacilli in such effusions. Fishberg (1) states that while some are sterile, in a large proportion tubercle bacilli may be found in ordinary smear preparations. By animal inoculation the vast majority are found to contain tubercle bacilli. On the contrary Ustvedt (2) finds that only in some cases can tubercle bacilli be demonstrated by guinea-pig inoculation. The complications which may arise when an effusion follows an artificial pneumothorax, even if the pneumothorax be a good one, are in many instances dangerous to the patient, prolong his period of hospital treatment, and may be permanently disabling in proportion to the loss of vital capacity and respiratory function which they produce.

This study was undertaken in Robroyston Sanatorium, Glasgow. During the investigation the patients admitted suffered mainly from moderately advanced or far advanced pulmonary tuberculosis. A detailed study of fifty patients whose pneumothoraces had recently been induced and were likely to be maintained was made. In addition, specimens of pleural fluid were examined from an additional group of twenty-five pneumothorax-treated patients. In the first group of fifty patients full blood examinations were carried out at fortnightly intervals except when an effusion was thought to be imminent when they were done at weekly intervals. These weekly examinations were maintained during the development of the effusion but as the patient's condition became stabilised they were again done at longer intervals. In the second group of twenty-five patients no blood examinations were performed.

In order to have a standard for comparison of patients in this series with those of other workers, the Classification of the National Tuberculosis Association of America, as modified by Salkin and Cadden (3), was adopted. Their subdivision of the minimal and moderately advanced groups was not employed however. The writer has also appended the type of tuberculous disease predominating in each patient. The group of patients not developing a pleural effusion will be

<sup>1</sup> From Robroyston Sanatorium, Millerston, Glasgow, Scotland.

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referred to as Group A and those developing an effusion will be referred to as Group B. From table 1 it will be seen that 12 per cent more patients of Group B fall into the far advanced classification. Again 58 per cent of Group B patients fall into subgroups 4 and 5 of Salkin and Cadden's classification whereas only 33 per cent of Group A patients fall into these subgroups. Also Group B manifests a preponderance of patients with symptoms allocating them to symptom Group C, 65 per cent as against 17 per cent for Group A. These findings suggest that the farther the disease has advanced in the lungs and the more severe the impairment in function, the more likely is a pleural effusion to arise in the course of artificial pneumothorax therapy. This is a finding already well known. Packard, Hayes and Blanchet (4) state that "the more active and acute the pulmonary lesion the more frequent and more serious is the pleurisy." From table 1 it is seen that by adding together the percentages of patients having the

TABLE 1

*Classification of patients according to extent of disease, symptoms and type of disease*

CLASSIFICATION	GROUP A		GROUP B	
	No.	Per cent	No.	Per cent
Moderately advanced.....	8	35	12	23
Far advanced.....	15	65	40	77
Symptom group A.....	2	9	1	2
Symptom group B.....	17	74	17	33
Symptom group C.....	4	17	34	65
TYPE OF DISEASE				
Caseous.....	1	4	3	6
Caseo-cavernous.....	12	52	27	52
Fibrocaceous.....	8	35	9	17
Fibroecavernous.....	2	9	13	25

more active types of disease, Caseous, Caseo-cavernous and Fibrocaceous 91 per cent occur in Group A and 75 per cent in Group B. It therefore follows that in this series of seventy-five patients, although a high percentage of patients developing a pleural effusion had an active and acute lesion, it is important to realise that many patients with similar lesions did not develop an effusion. This finding does not invalidate the statement quoted but indicates that it is necessary to investigate the more thoroughly other contributory causes in patients developing effusions. It is, too, a very important finding for Pinner (5) states that "acute caseous-pneumonic progressive involvement is frequently considered to be an absolute contraindication, mainly on account of the real danger of empyema." The writer's observation would tend to support Pinner's suggestion that treatment of patients having this type of lesion will occasionally save lives which would soon be lost without any collapse treatment.

It may be concluded from the evidence presented that the extent and acuteness



of the pulmonary lesion have a considerable influence on the development of a pleural effusion once an artificial pneumothorax is induced. This being so, it might be expected that the degree of pleural involvement, especially by recent tuberculous infiltration, would bear a similar relationship to the incidence of effusions. The means available for assessing this are the history, skiagrams and thoracoscopy.

It was noted that the percentage of patients with a history of less than one year from the onset of symptoms till the induction of a pneumothorax was 78 per cent for Group A and 87 per cent for Group B. In six patients of Group A and twenty-two patients of Group B, symptoms or signs suggestive of pleurisy were noted at varying intervals before the pneumothorax induction. An interval of six months or less was recorded in 44 per cent of the patients of Group A and for Group B the corresponding figure was 80 per cent. The effusion group therefore has a slight predominance of patients whose history is less than one year and a definite predominance of patients whose pleura has been recently involved in the tuberculous process.

TABLE 2  
*Subgrouping of far advanced patients*

	GROUP A		GROUP B	
	No.	Per cent	No.	Per cent
Subgroup 1.....	3	20	1	2
Subgroup 2.....	1	7	10	25
Subgroup 3.....	6	40	6	15
Subgroup 4.....	4	26	21	53
Subgroup 5.....	1	7	2	5

From the examination of skiagrams and from thoracoscopic findings it was noted that a high percentage of pneumothoraces in each group were complicated by adhesions—92 per cent of Group A and 94 per cent of Group B had adhesions present. To account for the high incidence of adhesions in the dry group it is necessary to know something of their pathology and that of the lung adjacent to them. Unfortunately several patients in each group did not have a thoracoscopy performed. The figures and the percentages given in table 3 are based on such a small number of thoracoscopic examinations in each group, that they cannot have any great significance. However, the general trend of the findings may be noted. Evidence of subpleural involvement of the lung as shown by the presence of tubercles is more frequent in the effusion groups. These tubercles are, in all probability, of recent origin, for had they appeared before the induction of a pneumothorax, pleural adhesions would probably have formed. The percentage of the larger and more complex adhesions is much the same in both groups, but in Group B the incidence of adhesions containing lung parenchyma is considerably higher than in Group A. It would appear that the presence of subpleural lesions may have some influence on the occurrence of effusions and so

also may the presence of lung in the pleural adhesions. The lung tissue extending into such adhesions will often be the seat of tuberculous disease and therefore a potential source of tubercle bacilli. In addition, tubercle bacilli may be liberated from the lymphatic spaces present in adhesions of recent origin, if these be punctured.

Thus, in general, the shorter the duration of the patient's history of active disease in the lung parenchyma or pleural cavity, the more numerous and complex the adhesions in the pneumothorax and the more often that subpleural tubercles are seen, then the more often do pleural effusions occur. One does not find much information in the literature to confirm the first observation as relevant statistics are lacking. However, many authors are agreed that the more numerous and complex are the adhesions present in a pneumothorax, the more frequent will be the complication of fluid formation. Among such workers may be mentioned Davies (6), Goorwitch (7) and Simmonds (8). The latter

TABLE 3  
*Summary of thorascopic findings*

NUMBER	GROUP A		GROUP B	
	No.	Per cent	No.	Per cent
	11		25	
Pleural tubercles present.....	2	18	10	40
Lung tissue observed in adhesions....	4	36	14	56
Type of adhesions.				
Strings and cords.....	3	27	6	24
Bands and curtains.....	8	73	19	76
Number cut.....	6		17	

states that "effusion is twice as common when adhesions cannot be completely freed as when a free pleura is obtained." Concerning the observation that recent subpleural involvement of the lung is associated with fluid formation in a pneumothorax, the writer finds various workers in complete agreement with this finding. In fact, Packard, Hayes and Blanchet (4) state "it would seem that the most common pathogenesis of pleural exudate in man is the direct extension of an active subpleural focus through the allergic visceral pleura. By the aid of the thoracoscope subpleural tubercles are frequently seen and occasionally patches of exudate on the pleura have been observed."

Unfortunately the space created by the operator when he induces an artificial pneumothorax is quite uncontrollable. It is widely recognised that the degree of lung collapse attained following induction of a pneumothorax is often greater than can be accounted for by the amount of air introduced. This being so, it might be expected that the spread of tuberculous infection to the pleural cavity would be most likely to occur in the earlier months of treatment when adhesions are being stretched and caseating tubercles may easily rupture into the pleural cavity. This is borne out by the following figures. By the end of

six months of pneumothorax treatment 70 per cent of the patients of Group B had developed effusions and by the end of twelve months this figure had risen to 91 per cent. Peters and Wooley (9) give very similar figures, offering 76 per cent within six months and 95 per cent within twelve months, their total number of patients with effusions being seventy-nine.

Having observed that pleural effusions usually occur during the early months of pneumothorax treatment when tuberculous lesions, pleural or pulmonary, are still in an active state, it is opportune to consider now the mechanism of their production.

There is some difference of opinion as to what is the immediate precipitating factor. Bard (10) is convinced that practically all severe pleurisy is due to pleuro-pulmonary perforations but Dumarest, quoted by Packard, Hayes and Blanchet (4), could find no evidence of bronchopleural fistulae on observing the manometric pressures in patients developing pleural effusions. The writer observed that the average mean pressure readings taken during the period when the effusion was developing showed an increase in 71 per cent of the patients. Ford (11) believes that pleural effusions complicating pneumothorax are due to the breaking down of adhesions. Gloyne (12) considers that if an adhesion be ruptured at a point at which tubercle bacilli can be liberated into the pleural sac, a secondary effusion is likely to follow and this is, he states, probably what happens from time to time in pleural effusion complicating pneumothorax. Wollaston (13) thinks that the stress imposed on a diseased area of lung by the presence of adhesions is of such importance in the causation of a pleural effusion that he is prepared to perform thoracoscopy and adhesion section if it be possible, even in the presence of an acute effusion. Korol (14) points out also that a haemorrhagic effusion may result from bleeding of the stump of a torn adhesion or from a progressive ulcerating tuberculous lesion in the lung extending to a point where it may involve the visceral pleura and a large blood vessel. Such a happening is rare but it is apparently not so uncommon for a caseating subpleural focus to extend into the pleural cavity. Matson, Matson and Bisailon (15) infer from a study of empyema occurring during pneumothorax therapy that a subpleural tuberculous lesion is of more importance in producing an empyema than is the tearing of lung cortex, for adhesions were absent in 50 per cent of their empyema cases. Goorwitch (7) is of a similar opinion stating that "the clinical manifestations of a pleural effusion occurring during pneumothorax therapy probably depend to a high degree on the quantity of caseous tissue and tubercle bacilli spilled from superficial ulcerative pulmonary lesions into the pleural sac." Simmonds (8) in noting that pleural effusion was seven times more frequent in pneumothorax-treated patients compared with those not so treated, suggests that this is due to the opening of the lung spaces, especially pulmonary cavities, into the pleural cavity. Hutchinson and Blair (16) hold a similar belief, supporting their view by the fact that a rise in intrapleural pressure often precedes a pleural effusion and the temperature which accompanies its development is very similar to that seen in ordinary cases of spontaneous pneumothorax. The clinical findings in this series may assist in elucidating the mechanism of the production of these effusions.

An analysis of the findings presented leads to several conclusions:

1. In a high percentage of patients a systemic upset coincides with the onset of a pleural effusion. This upset is generally accompanied by fever of varying degree and a fall in blood pressure and in weight may also occur. The latter generally appear when the systemic disturbance and fever are most severe but this is not invariable.

2. Dyspnoea is present in a considerable proportion of patients. This lends support to the theory that in many of these patients a spontaneous pneumothorax occurs before the onset of an effusion.

3. Increased cough and spit although not occurring so frequently as dyspnoea are nevertheless noteworthy in quite a number of patients, 38 and 36 per cent respectively. These also may indicate that air has escaped into the pleural cavity for often increasing collapse of the lung is associated with an increase in cough and sputum.

TABLE 4  
*Clinical findings observed during evolution of effusion*

	<i>per cent</i>
Systemic upset.....	76
Dyspnoea.....	64
Pain.....	52
Increased cough.....	38
Increased sputum.....	36
Fall in weight.....	42
Fever.....	86
Fall in blood pressure.....	47

4. Pain in the chest was noted in 52 per cent of patients. Additional evidence of the inflammatory state of the pleura is shown by the observation that pleural puncture at this time produced more severe pain than previously had been experienced by most patients. Further confirmation of pleural inflammation is provided by the systemic upset and fever previously recorded.

Considering the clinical findings noted, it is obvious that in a majority of patients the onset of a pleural effusion during artificial pneumothorax therapy is accompanied by a syndrome such as might be produced by the exacerbation of tuberculous disease within the pleural cavity. The increase in intrapleural pressure observed in 71 per cent of patients is strongly suggestive of the addition of air to the pneumothorax. This air, as previously explained, can have been added only by the rupture of lung tissue. This may have taken place by the perforation of a cavity or the ulceration of a subpleural caseous focus with or without the drag of an adhesion on the area rupturing. Bard (10) has demonstrated that such lung ruptures are often valvular. In those patients showing no change in intrapleural pressure, tubercle bacilli may have entered the pleural cavity from ulceration of a caseous area or from the rupture of recent adhesions which Gloyne (12) has shown may contain tubercle bacilli. In four patients the writer observed a fall in intrapleural pressure during the development of an effusion and

this, he suggests, may have been due to an increased absorption of air, no spontaneous pneumothorax having occurred in these patients. Pinner, Moerke and Saley (17) state that inflammation increases the permeability of capillaries and endothelial linings and that this mechanism must be assumed for the pleura. Up to this point, quoted authority and the present investigation show that whatever the change in the pleural cavity, it has its origin in the almost unnatural separation of the pleural layers whereby stresses are put on adhesions, support is taken away from lung cavities, and subpleural tubercles which, in nature, might have resulted in further adhesions, find themselves literally out of touch with the parietal pleura. From any of these sources the shedding of tubercle bacilli on to the allergic pleural surfaces will be ample enough cause for the development of an effusion. It follows that the finding of tubercle bacilli in the effusion should

TABLE 5

*Results of examination for tubercle bacilli of pleural fluid from fifty-two patients*

	NO. OF PATIENTS	PER CENT OF PATIENTS
1. Direct smear positive .....	37	71
2. Direct smear negative but antiformin concentration smear positive .....	3	6
3. Cultures positive when methods 1 and 2 were negative .....	4	8
4. Guinea-pigs dying from tuberculosis when methods 1, 2 and 3 were negative .....	3	6
5. Total number of patients with tubercle bacilli in pleural effusion.....	47	90

Note: Forty-two patients had positive cultures and of these thirty-eight had positive smears. On one occasion a culture was positive when guinea-pig inoculation proved negative but a later specimen of fluid from this patient was positive on direct smear and on guinea-pig inoculation.

be an almost constant occurrence and with the questions raised by these thoughts the following paragraphs are intended to deal.

A combination of three methods was used in the search for the tubercle bacillus.

1. Examination of smears made from the centrifuged sediment of each effusion. Five ounces of citrated fluid were usually centrifuged. A smear prepared by the antiformin concentration method was examined if the direct smear was negative.

2. Culture of the sediment on Lowenstein's medium (one bottle).

3. Guinea-pig inoculation when necessary.

From table 5, conclusive proof of infection of the pleural cavity by tubercle bacilli is demonstrated in 91 per cent of the fifty-two patients who had an effusion. Direct smear revealed tubercle bacilli in 71 per cent of patients and this figure increased to 77 per cent when examination of smears prepared by the antiformin concentration method was included. Doubtless the percentage would have been improved upon by using the Chlorux method for the examination of the sediments, supplemented by fluorescent microscopy. These aids were not available

in the hospital laboratory at the time of the investigation. However Lowenstein's culture medium increased the percentage of positive results to 85 per cent. Guinea-pig inoculation finally increased the average percentage of positive results to 90 per cent.

In view of these findings, it is rather surprising to find Ustvedt (2) stating in his handbook of pulmonary tuberculosis published in 1942 that "the cause of effusions occurring in artificial pneumothorax is not yet established." Despite this, he remarks that "presumably in most cases the tuberculous process spreads to the pleura and involves its surface." On the other hand Brock, Mullen and Woodson (18) found tubercle bacilli in 100 per cent of twenty-eight of these effusions and they state that "effusions developing subsequent to the collapse of tuberculous lungs are not only always tuberculous in nature but tubercle bacilli can be found in nearly every case if the proper procedure of examination is followed." They used direct smear examination, culture and guinea-pig inoculation but they do not give the percentage of positive results achieved by each method. Other workers whose opinion is that these effusions are tuberculous in nature include Burrell (19), Davies (6), Peters and Wooley (9), Alexander (20) and Goorwitch (21).

Turning next to the cytology of these effusions we find Gloyne (22) stating that "the mild serous effusions have much the same characters as the secondary serous effusions of frank open pulmonary tuberculosis, show a lymphocytic predominance in the cell count with three per cent of protein or more, and are sterile on culture. As the fluid becomes more opalescent and reaches the sero-purulent stage the polymorphs increase and finally dominate the picture." Gloyne also believes that if there are many polymorphs together with tubercle bacilli, this is strong presumptive evidence of a spontaneous pneumothorax. In the writer's series 76 per cent of the effusions showed a lymphocytic predominance and 24 per cent showed a predominance of polymorphs at the initial examination. Of those patients in whom the polymorphs predominated, most showed tubercle bacilli in considerable numbers in a direct smear, but only one third of these patients showed evidence of spontaneous pneumothorax. The cytology confirms Burrell's (19) contention that these fluids are exudates and agrees with Gloyne's description of the cellular types found. In addition, the cytological examination lends support to the theory of the tuberculous basis for these effusions.

Specific gravity estimations gave readings varying from 1005 to 1026. All the effusions gave a positive Rivalta's test for serosamucin and the Esbach readings varied between 1.8 and 4 per cent of protein. Thus some of the fluids possessing the characters of exudates also showed the physical characteristics of transudates. Pinner, Moerke and Saley (17) had similar findings in their series of thirty-two specimens. It is the writer's belief that these physico-chemical findings are of little help in elucidating the aetiology of the effusions under consideration.

Having established beyond doubt the main causative factor for these effusions we may now consider the predisposing factors stressed in varying degree by different writers.

## 1. TRAUMA

No *external* trauma was sustained by any patient. *Internal* trauma may take several forms such as the use of positive pressures and excessive amounts of air, the giving of air by inexperienced operators when inadequate manometric oscillations have been recorded, too rapid introduction of air, rough introduction of large needles, thoracoscopy and adhesion section.

In this hospital Clive Riviere needles are used for the induction and first refill. Next, an aspiration type of needle 1.5 mm. in diameter and having a side opening near the point, is used till the lung is sufficiently collapsed to allow of the use of Kjer-Petersen needles without serious risk of puncturing it. Anaesthesia using 2 per cent novocaine is employed except when Kjer-Petersen needles are used.

When in hospital the patients under consideration did not receive amounts of air in excess of 400 cc. and generally refills averaged 200-300 cc. twice weekly for the first few months of pneumothorax treatment. At the outpatient clinics of the city some of these patients later had refills of 500-1,000 cc. at intervals of three to six weeks. Only one patient developed an effusion while under this regime. The trauma produced by large refills varies from patient to patient and large infrequent refills are certainly contraindicated in those pneumothoraces in which adhesions are present.

In relation to the use of positive intrapleural pressures the writer finds on reviewing his records that the maximum positive readings were recorded in the non-effusion group and in addition this group had a greater number of patients with average readings above zero, this being most marked after refills. It may therefore be suggested that positive intrapleural pressures per se have not, in this series, proved to be so important as many writers suggest in the aetiology of pleural effusions. Packard, Hayes and Blanchet (4) confirm this observation and so also do Peters and Wooley (9). Davics (6), Rosenthal (23), Leaver and Hardaway (24), among others, believe that positive intrapleural pressures are of importance in the causation of pleural effusions in artificial pneumothorax. It may be concluded that in certain patients the use of positive intrapleural pressures may predispose to the development of an effusion; probably the excessive pressure leads to the damage of superficial areas of recent disease in the lung especially if adhesions are attached there. Peters and Wooley (9) suggest that adhesions pulling on a thin-walled cavity may lead to cavity rupture and fluid formation but this will usually be purulent.

Concerning the introduction of air when inadequate manometric oscillations have been recorded, it may be noted that resident doctors are instructed to obtain a free swing of at least five centimetres on the manometer before introducing air. In addition, air is introduced with the manometer still in the circuit so that air cannot be introduced too rapidly. These two factors are therefore unimportant in this series.

Thoracoscopy was performed in eleven patients of Group A and in twenty-five patients of Group B. In Group B fourteen patients developed an effusion at some date afterwards but in only five of these did fluid appear in the ensuing three months. Only two of these five patients had adhesions cut. In only one of

the five did the fluid not become purulent. The surgeon who performed these operations was convinced that it was the state of the pleura and not his intervention which was responsible for these effusions and the empyemata which ensued. Support is lent to this contention by the appearance of fluid in two patients who had no adhesions cut. On reading the review of the literature given by Goorwitch (21) on this subject, one is impressed by the post-operative interval regarded by different workers as significant. Smart is quoted as stating that empyemata occurring one month to two years after operation may possibly be related to it. On the contrary Wollaston (13) believes that operation is not responsible in the majority of cases for any empyema that may follow it and he reports an incidence of 19.5 per cent of pleural effusions following two hundred pneumolyses, 2 per cent of tuberculous empyemata and 0.5 per cent of mixed

TABLE 6  
*Relation between thoracoscopy, pneumolysis and empyemata*

NO. AND INITIALS OF PATIENT	DURATION IN MONTHS BETWEEN THORACOSCOPY AND EMPYEMA	FLUID PRESENT AT OPERATION	NO FLUID PRESENT AT OPERATION	ADHESIONS CUT	THORACOSCOPY ONLY
6. A. R.....	6		x	x	
18. M. A.....	18		x		x
21. A. P.....	25		x	x	
22. S. S.....	1½		x		x
25. M. McA.....	6		x	x	
11. A. H.....	7	x		x	
15. E. W.....	4	x		x	
23. M. B.....	3	x		x	
39. M. F.....	3	x		x	
43. J. B.....	1½	x		x	

empyemata. In this series of fifty-two patients five developed an empyema at some time following thoracoscopy, no fluid being present at the time of the operation; another five patients having a serous effusion at the time of operation later developed an empyema and in two patients purulent fluid was present before operation and persisted after it. From thirty-six thorascopies the incidence of empyemata following operation is 28 per cent, a significant increase on the figure given by Wollaston. This high figure lends support to the statement made by Benjamin (25) that thoracoscopy should not be done during an acute pleurisy. Jacobaeus (26) also stated that in patients having a serous pleurisy prior to operation the outlook was not so favourable because such pleurisy usually became worse after the surgeon's intervention. In this series, of thirteen patients whose pleura was inflamed at the time of thoracoscopy, ten developed empyemata and three developed serous effusions which later cleared satisfactorily. Perhaps the heat generated by the lamp of the thoracoscope and/or the cautery when used, or the possible perforation of tubercles in the parietal pleura by the trocar and cannula, may have had some effect in producing these effusions.



The conclusion cannot be avoided that thoracoscopy and adhesion section may have some influence on the development of a pleural effusion, especially a purulent one. Adhesion section, even when it results in a good collapse of the lung, should not be readily undertaken if serous fluid is already present in the pleural cavity or if the pleura be inflamed.

Further factors predisposing to pleural effusions are given in the following paragraphs.

## 2. EXERCISE

Both Burrell (19) and Wingfield (27) state that exercise has not in their experience been a predisposing cause of pleural effusion during artificial pneumothorax. 53.8 per cent of the effusions in this series occurred in the first three months of treatment, a time during which bed rest was strictly enforced. By the end of six months treatment, 69.2 per cent of the pleural effusions had developed and exercise, if permitted, was still restricted, the patient being allowed up for one to two hours per day at the most. It may be presumed that exercise was of little importance in this series as a predisposing cause of pleural effusion.

## 3. SEASON AND INTERCURRENT INFECTION

In this series 67 per cent of the effusions occurred in the winter months of October to March. This is in accordance with Peters and Wooley's (9) findings but Burrell (19) is quite emphatic in stating that weather has little influence on the causation of pleural effusions. Some authors believe that intercurrent infections predispose to pleural effusions in pneumothorax-treated patients, and the fact that in this series the highest incidence of effusions fell during the winter months of the year, when minor infections are most common, may lend some support to this idea. However, on analysing his data further the writer found that in each quarter of the year the majority of effusions occurred within the first six months of treatment. Thus before finally incriminating any season one must take the relatively more important factor of duration of pneumothorax treatment into consideration.

## 4. MENSTRUATION

Menstrual hyperaemia is believed by some workers to be of importance in the causation of effusions (4). In Group B notes relative to menstruation are available for twenty-four patients. Of these only four menstruated within a period of five days before or after the onset of an effusion. It appears that in this series menstruation was of little importance as a subsidiary factor in the causation of an effusion.

## 5. THE GAS

All patients received air at room temperature. Burrell (19) finds that the gas employed matters not at all nor does heating the air as it is given have any beneficial effect. Portas and Corallo (28) using ozone instead of air had no effusions in a series of forty-two artificial pneumothoraces.

## 6. ALLERGY

It has been amply demonstrated in experimental animals that the introduction of tubercle bacilli into the pleural cavity of those previously sensitised by subcutaneous inoculation of tubercle bacilli, results in the formation of a pleural effusion, (Lemon and Feldman (30)). All the patients under review suffered from pulmonary tuberculosis and it has been demonstrated that 90 per cent of the fifty-two effusions investigated contained tubercle bacilli. It is not unreasonable to postulate that allergy played as important a part in these subjects as it did in experimental guinea-pigs and rabbits. Wingfield (31) notes that the tissues which are close to a focus of previous disease appear to be more allergic than those further distant. This is probably of importance in the aetiology of pleural effusions. Baum (32) quotes Neumann of Vienna, who states that the amount of fluid formed during artificial pneumothorax treatment can be reduced to a minimum by the systematic use of tuberculin in every case and Baum believes that some form of specific treatment is indicated when an appreciable amount of fluid has been formed during artificial pneumothorax therapy. Allergy then must be considered of practical importance in the causation of pleural effusions.

## 7. MISCELLANEOUS FACTORS

### *a. Circulatory Disturbance*

Disturbance of the circulation within the chest would seem to be of little importance except in so far as too sudden compression of a diseased and congested lung may lead to excessive passive congestion. Rao (33) advances this theory but Alexander (20) quotes several workers who have shown that the collapsed lung contains less blood. This pleural fluid should however be a transudate. Complete collapse of a non-tuberculous lung by spontaneous pneumothorax does not give rise to a pleural effusion.

### *b. Calcium Deficiency*

Pisani and Smejkal (34) have suggested that calcium deficiency may play a part in the aetiology of these effusions. No drugs were employed in this series of patients.

### *c. Phrenic Crush*

None of the fifty-two patients had a phrenic crush done on their pneumothorax side and I can give no opinion as to its value. Lilienthal (35) quotes Sauerbruch who believes that phrenic crush is beneficial in preventing the formation of effusions.

## SMALL TRANSITORY EFFUSIONS

It is the belief of most workers in the field of artificial pneumothorax that in practically every patient small transitory collections of fluids in the costo-phrenic sinus and insufficient to cover the hemi-diaphragm will be seen by fluoroscopy if this be carried out sufficiently often. Dumarest is quoted by Packard, Hayes

and Blanchet (4) as referring to these small effusions under the heading "Benign Pleurisy". Other writers classify them among what they term "cold effusions". Among such investigators is Rao (33). Figures given by various writers for the incidence of these small effusions vary from 12 to 100 per cent. The writer found 16 per cent of them in the first group of fifty patients examined; 8 per cent occurred in patients whose pneumothorax was not complicated by a typical tuberculous effusion and 8 per cent in patients who later had a tuberculous effusion. No doubt this lower percentage would have been higher had more frequent fluoroscopy been carried out; on the average, only fortnightly screen examinations were performed owing to pressure of work. Stivelman and Rosenblatt (36) state that "these effusions are of no consequence, do not affect the intrapleural pressure, need no special treatment and that insufflations should be given as if there were no effusion." The findings in this series were similar. No tubercle bacilli or other organisms were found in any of the four small effusions which it was possible to aspirate. The results of Rivalta's test, Esbach readings and specific gravity estimations were conflicting and did not prove whether the effusions were transudates or exudates. The most important finding is the absence of tubercle from these effusions.

#### THE EMPYEMATA

There is some difference of opinion as to what constitutes a tuberculous empyema. Some writers would include any pleural fluid containing tubercle bacilli while others not only insist on frank pus being present, but include in their definition the clinical picture which accompanies its formation and subsequent course. In this study Dickey's (37) definition is employed. He states that any sero-purulent or purulent fluid containing tubercle bacilli is, in his paper, classed as a tuberculous empyema.

Their aetiology is closely linked with that of serous effusions occurring during artificial pneumothorax therapy, for many empyemata develop from such effusions. According to Peters and Wooley (9) it was Brauer and Spengler who were among the first to observe the evolution of a clear serous effusion into an empyema. Packard, Hayes and Blanchet (4) believe that almost always a tuberculous empyema is preceded by a serous effusion during treatment by artificial pneumothorax. Keers and Rigden (38) note that the change from a serous effusion to a frank empyema occurs at a varying interval according to the severity of the pleural infection. Leaver and Hardaway (24) found on investigating the records of seven hundred and fifty patients treated by artificial pneumothorax that 5.8 per cent developed empyemata. Of these patients, twenty-one or 60 per cent had a superimposed spontaneous pneumothorax and fourteen or 40 per cent had a clear fluid in the absence of a demonstrable spontaneous pneumothorax, before the empyema appeared. They note, however, that following a superimposed spontaneous pneumothorax with an open fistula, the pleural exudate is generally first serofibrinous in character although it soon becomes cloudy and later becomes frank pus. It is not necessary for a frank bronchopleural fistula to exist, for Coryllos (39) has noted that a high incidence of punc-

tiform fistulae, which quickly seal over, can give rise to pure tuberculous empyema.

It has been noted previously that tubercle bacilli may be liberated into the pleural space by the ulceration of a subpleural focus through the visceral pleura, by rupture of the wall of a cavity or by the tearing of an adhesion. Many workers have found that empyemata are prone to occur in mechanically unsatisfactory pneumothoraces. Among such may be mentioned Dickey (37) and Shields (40). Leaver and Hardaway state that post-mortem findings show that the site of rupture of subpleural lesions is most often near the pulmonary attachment of pleural adhesions and Gordon (41) quotes Alexander, among other workers, as noting that tubercles of the pleura are often found in considerable numbers at the base of adhesions. It is obvious that the tension put on such adhesions by large refills of air and coughing, may so damage the lung at the pulmonary attachment of an adhesion, that tubercle bacilli may be liberated quite easily into the pleural space. The lymphatic drainage of the pleural portion of the lung is towards the pleura and this, too, facilitates infection of the pleural space.

Several writers are agreed that the more acute types of tuberculosis are liable to be followed by empyemata should pneumothorax treatment be attempted. Hayes' (42) patients all suffered from far advanced disease, and a higher proportion of those with more recent disease developed empyemata than did those whose disease was of long duration. Matson, Matson and Bisailon (15) found that of fifty-nine empyemata in their series, twenty-nine developed in satisfactorily compressed cases and thirty in partially compressed cases. They remark that empyemata occurred in each clinical group which they used in classification of their patients very much in proportion to the duration of the pneumothorax, except in those patients who suffered from severe acutely infiltrating disease. Twenty-three per cent of empyemata occurred in this group and only 26 per cent of those patients were under treatment for more than one year. Shields (40) however in studying early therapeutic pneumothorax performed in fifty-two patients afflicted by tuberculous pneumonia, found that it did not increase the percentage of tuberculous empyemata. The writer's findings will now be presented.

Only one patient had a frank broncho-pleural fistula. Another patient had a tuberculous empyema later contaminated by *Staphylococcus Albus* during aspirations.

Twenty-one patients of Group B developed empyemata thus giving an incidence of forty per cent for the fifty-two patients having effusions. The incidence of empyemata in the fifty patients whose pneumothorax treatment was observed closely from the time of induction is 24 per cent, a figure somewhat above the average. The incidence given by a few other workers is shown in table 8.

The high incidence of empyemata in the writer's series is due undoubtedly to the large number of patients having advanced and/or acute tuberculosis. It is notable that the majority of the patients fell within the most far advanced

groups of Salkin and Cadden's classification. In addition most of these patients suffered from considerable constitutional upset on admission to hospital, twelve

TABLE 7

*Classification of patients developing empyemata and notes relating to their pneumothorax*

	NUMBER OF PATIENTS
Classification	
Moderately advanced.....	2
Far advanced I.....	1
Far advanced II.....	6
Far advanced III.....	0
Far advanced IV.....	11
Far advanced V.....	1
Symptom group	
Group A.....	0
Group B.....	4
Group C.....	17
Type of disease	
Casco-cavernous.....	12
Fibro-cascous with cavitation.....	2
Fibro-cavernous.....	7
Adhesions	
Present +.....	4
Present ++.....	17
Preceding serous effusion.....	20
Attributable to operation.....	2

Note: Present + indicates few and divisible adhesions. Present ++ indicates many and indivisible adhesions.

TABLE 8

*Incidence of empyemata during pneumothorax treatment as recorded by various authors*

NAME OF AUTHOR	NO. OF PATIENTS	INCIDENCE
		<i>per cent</i>
Leaver and Hardaway (24) .....	750	5.8
Unverricht, quoted by Ustvedt (2) .....	2,893	1.1
Matson, Matson and Bisailon (15) .....	480	12
Nalbant (43).....	20	35
Dumarest, quoted by Packard, Hayes and Blanchet (4). .....	247	17

of the twenty-one having a very acute type of disease. Some of these patients were in fact admitted as cases of pneumonia. These findings coincide with the reports of workers previously quoted.

It has been noted that many pneumothorax operators find that empyemata are prone to occur in ineffective pneumothoraces. This, too, was the writer's experience, for all of the twenty-one patients developing empyemata had also adhesions present which were so large in all but four patients as to make the pneumothorax only partially effective. In these four patients the adhesions were cut, one requiring two sessions. The findings of Matson, Matson and Bisailon (15) that 50 per cent of their empyemata occurred in satisfactorily compressed cases cannot be ignored. Doubtless, involvement of the visceral pleura by recent tuberculous infiltration could account for this. Of twelve patients of Group B on whom thoracoscopy was performed, seven showed visceral pleural tubercles, but no note was made by the surgeon in three of the remaining five patients as to whether tubercles were present or not. When tubercles were seen they were present in considerable numbers, except in two patients. It may therefore be taken as proven that in every patient who developed a tuberculous empyema the pleura was involved as indicated by the presence of pleural tubercles or adhesions.

Ninety per cent of the empyemata in this series developed in patients who previously had a serous effusion. Goorwitch (7) describes the treatment of twelve patients with empyemata all of which were preceded by serous effusions and Packard, Hayes and Blanchet (4) state that "tuberculous empyema almost always is preceded by or develops from a serous effusion." They found that in thirty-two patients with mild empyemata, the transition to pus was not recognised clinically in twenty-eight. Alexander (20) notes that a pure tuberculous empyema may occur at any time during pneumothorax therapy but that in patients suffering from acute exudative or pneumonic tuberculosis it may appear soon after the induction of pneumothorax. In these patients the fluid is usually purulent from its onset or becomes so rapidly. Empyemata which occur later in the treatment are however usually preceded by serous effusions. It is to this latter group that almost all of the writer's patients belong. Leaver and Hardaway (24) found however that only 40 per cent of thirty-five patients developed empyemata from serous effusions in the absence of signs of spontaneous pneumothorax. Alexander (20) continues that the time taken by a serous effusion to change into pus varies but that it may occur within three months. In the present series the shortest time was one month and the longest was fifteen months. Most patients developed an empyema three to five months after the onset of a serous effusion and it was noted that this effusion was usually moderate or large in size—i.e., up to or over five finger-breadths of fluid lying in the pleural cavity. At the onset of the serous effusion constitutional upset was often marked and fever of over 100°F. was usually recorded. However, the change to pus formation was not accompanied by gross signs of clinical deterioration except in two patients both of whom had bilateral disease and who ultimately died from it. Also the writer found that serial haemograms, of which over one thousand were performed in this investigation, were of little value in following the changes which took place in the effusions.

It was thought that the cytological and bacteriological examination of the

serous effusions themselves, might be of some value in determining which of them would later become purulent. On scrutinising the cell counts and the results relating to the finding of tubercle bacilli on direct smear in the earliest samples of fluid obtained, it is found that empyema formation generally occurred in those patients having a high neutrophil percentage, together with tubercle bacilli easily found on direct smear. The neutrophil percentage was generally over 40 per cent or if lower it rose steadily in successive specimens of fluid aspirated. Of ten patients with a high initial neutrophil percentage, seven developed empyemata. In all these patients tubercle bacilli were readily demonstrated in the first specimen of fluid aspirated. Of three other patients, in two of whom the initial neutrophil percentage was high (67-77 per cent), and in a third whose initial neutrophil count was 37 per cent, serous fluid persisted and finally cleared with repeated aspiration, pleural obliteration occurring in all. One of these patients with a high neutrophil percentage had tubercle bacilli easily found but in the other two patients they were found with difficulty. Of fifteen patients with a high initial lymphocytic percentage, four developed empyemata but in only one of these four were tubercle bacilli easily found on direct smear. Later specimens from these four patients showed a sudden increase in the neutrophil percentage together with an increase in the number of tubercle bacilli demonstrable. Of the eleven remaining patients, in four, tubercle bacilli were easily demonstrated, in six, they were discovered only after prolonged searching and in one they were not found even on culture and guinea-pig inoculation.

It would seem then that we have available in any sanatorium a simple yet reliable method which can assist materially the conduct of pneumothorax treatment. Should an effusion initially contain tubercle bacilli easily demonstrable on direct smear, together with a high neutrophil percentage, then this is strong evidence in favour of not submitting the patient to thoracoscopy for the pneumothorax will frequently have to be abandoned. Also, should these findings be confirmed in a large series of patients, we may be able to abandon, at an early date, many pneumothoraces on the basis of this examination, together with the other clinical findings. Thus might patients be spared the dangers of tuberculous empyemata and thoracoplasty be undertaken at a much earlier date.

The basic conditions under which an empyema may develop are advanced and acute pulmonary tuberculosis supplemented by artificial pneumothorax therapy which is often ineffective on account of adhesions. These basic factors may be supplemented by others. Leaver and Hardaway (24) mention the indiscriminate use of positive intrapleural pressures, intrapleural surgery, the use of oil for compression, pleuro-cutaneous fistula following the aspiration of a hydrothorax, errors of aseptic technique, neglected hydrothoraces and the sudden cessation of pneumothorax treatment in patients having a considerable lung collapse. Packard, Hayes and Blanchet (4) note that a serous effusion may become purulent during a cold or any septic infection. In this series the only factors which might have been of importance are the use of positive pressures, adhesion section and intercurrent infection.

On examining the records of manometric readings it is found that fifteen of the twenty-one patients developing empyemata had markedly positive pressures used before their empyemata appeared. The remaining six patients had their pneumothoraces abandoned following the development of a serous effusion and no further pressure readings were taken. It has previously been mentioned that in this series thoracoscopy and adhesion section were possible causes of some of the empyemata encountered. In five patients the change in character of the pleural fluid was preceded by a common cold. No organisms other than tubercle bacilli were present in the pleural fluid aspirated and the influence, if any, of the intercurrent infection would possibly be exerted by a diminution in the general resistance of the patient.

Another factor to be considered is allergy. It may well be the reason why some serous effusions become purulent while others remain serous and sometimes disappear quite unaccountably while still in that state. Packard, Hayes and Blanchet (4) state that "a silent pyothorax is perhaps due to the seepage of tubercle bacilli from a subpleural focus into the pleural cavity. Probably the pleurae have been rendered very allergic by the previous mild infections and a purulent effusion results." However, tuberculous empyemata are rare apart from artificial or spontaneous pneumothorax. Allergy therefore operates unfavourably to the patient on account of the fact that the physician has created a space within which many of the future happenings are without his control.

#### END RESULTS

The period of observation of this series of patients is at the maximum four and a half years and at the minimum four years.

It is seen from the table given that the patients in whom effusions developed had a considerably higher mortality rate than those whose pleural space remained dry. This increased mortality rate coincided with a high rate of pneumothoraces abandoned and with a failure to obtain sputum conversion.

In Group A, of nine patients whose pneumothoraces were abandoned, four died; all of these patients failed to obtain sputum conversion. In Group B, of forty-three patients whose pneumothoraces were abandoned, twenty-one died; sixteen of these twenty-one failed to obtain sputum conversion. These results need no comment.

It is interesting to note the mortality rate in each group in relation to the state of disease at the onset of treatment. No patient whose disease was moderately advanced died. For Groups A and B the mortality rate for patients with far advanced disease was respectively 26 and 50 per cent. All deaths in Group A were attributable to advancing bilateral pulmonary tuberculosis. In Group B the cause was similar except in four patients. One died suddenly following a spontaneous pneumothorax, another died two days after a thoracoplasty, and in the remaining two patients, tuberculous empyemata one of which was secondarily infected, accelerated their downward course. Thus only in three patients could a complication of pneumothorax treatment have had any important connection with the patient's death.



It was noted previously that the incidence of empyemata in the fifty-two patients comprising Group B was 40 per cent. The mortality rate for this group of patients having empyemata was 52 per cent whereas the mortality rate for patients having serous effusions only was 32 per cent. All deaths except one in the empyema group were attributable to advancing bilateral disease. That patient died ultimately from a secondarily infected empyema. Burrell

TABLE 9  
*End results of pneumothorax treatment*

DATA	GROUP A		GROUP B	
	No.	Per cent	No.	Per cent
Patients alive.....	18	78	30	57
Patients dead.....	5*	22	22	43
Artificial pneumothorax				
Maintained.....	2	9	4	8
Abandoned.....	9	39	43	83
Discontinued.....	12	52	5	9
Results				
Obliterative pleuritis.....	0		9	17
Serous effusion persisted and A.P. was maintained.....	0		1	2
Serous effusion disappeared and A.P. was maintained.....	0		6	12
Serous effusion persisted and A.P. was abandoned.....	0		15	29
Tuberculous empyema.....	0		19	36
Persisted.....	0		3	
Obliterative pleuritis.....	0		16	
Secondarily infected empyema.....	0		2	4
Persisted.....	0		1	
Obliterative pleuritis.....	0		1	

\* One killed after recovery, in street accident.

(44) in comparing the mortality rate in patients having serous effusions and in those having empyemata, found that the outlook was more serious when purulent fluid was present but that the mortality rate was high in all patients who suffered from extensive disease. Brock, Mullen and Woodson (18) found that serous effusions had little to do with the cause of death in their patients, and that those who developed empyemata did not have a higher death rate than those who developed only a serous effusion. They found that death was usually caused by progression of the pulmonary disease. The results in this series support Burrell's conclusions.

It is important to record that in only three patients did empyemata fail to

dry up and the underlying lung to re-expand with repeated aspirations. Thus 86 per cent of the empyemata were controlled. Salkin and Cadden (45) give a figure of 80 per cent for empyemata controlled similarly in a series of two hundred and twenty-five empyemata. Goorwitch (7) states that "major surgical treatment yields and will continue to yield a higher percentage of permanently successful results than aspiration or intrapleural medication." Four patients were treated for a short period by intrapleural injections of a Promanide solution but this treatment had to be abandoned owing to the deleterious effect on

TABLE 10  
*Final clinical results*

	GROUP A			GROUP B		
	Artificial pneumothorax					
	Main- tained	Aban- doned	Discon- tinued	Main- tained	Aban- doned	Discon- tinued
	Number of patients					
	2	9	12	3	43	6
Sputum						
Converted.....	2	4	12	3	22	6
Not converted.....	0	5	0	0	21	0
Number of deaths.....	0	4	1	0	21	0
Number alive and working.....	2	4	10	3	15	6
Number alive but unfit.....	0	1	1	0	7	0
Number having thoracoplasty.....	0	2	0	0	11	0
Results of thoracoplasty						
Alive and working.....	0	1	0	0	7	0
Alive but unfit.....	0	1	0	0	2	0
Dead.....	0	0	0	0	2	0

the patient's condition (46). Of twenty-one patients who had empyemata nine are now alive; five of these patients did not require further collapse after their lungs re-expanded but four required a thoracoplasty. Three of the patients not operated upon are working and two are unfit for work but are able to enjoy a very sedentary life. Two of the patients having thoracoplasty are working but the other two are unfit and have a poor prognosis owing to contralateral disease having developed.

In each group, patients whose pneumothoraces were either maintained till the present or discontinued by the physician benefited from their treatment and apart from two patients they are alive and well. One of these two is alive but unfit, and the other whose treatment had been concluded and who was working, was killed. Ten of these patients had unilateral disease and fourteen bilateral

disease, the better lung being treated by rest only, supplemented by phrenic crush or gold therapy in some patients. All obtained sputum conversion.

Of the seventy-five patients under consideration, pneumothorax treatment was abandoned in fifty-two. In nine patients of Group A whose pneumothorax was abandoned, two obtained some benefit from the treatment and no further collapse therapy was necessary. Both of these patients had partial pneumothoraces. Of seven patients who did not benefit from pneumothorax treatment all had partial pneumothoraces which were abandoned finally on that account. Two of these patients had thoracoplasty and as a result one is working but the other is unfit. One other patient who had no further treatment is also working but four others are dead. In Group B, of forty-three patients whose pneumothoraces were abandoned, thirteen obtained some benefit from the treatment and thirty obtained no benefit. Of the thirteen who benefited from treatment, ten had partial pneumothoraces and three had their lungs well collapsed after adhesion section. Three empyemata occurred in those having partial pneumothoraces and one among those having a good collapse. Two patients having a partial collapse later had thoracoplasty performed. All patients in this group are well and working. Of the thirty patients who did not benefit from pneumothorax treatment, fifteen had their pneumothoraces abandoned on account of empyemata and of these two had a good lung collapse following adhesion section. The remaining fifteen patients had partial pneumothoraces which were abandoned on account of adhesions. Of this group of thirty patients, nine had thoracoplasty performed and of these, four are alive and well, three are unfit and two are dead. Six of these patients had empyemata. Of the remaining twenty-one patients, twenty are dead and one is alive but expected to die soon from contralateral spread of the disease.

These results clearly illustrate the poor prognosis which an incomplete pneumothorax carries for only 29 per cent of the fifty-two patients whose pneumothoraces were abandoned obtained any lasting benefit from the treatment.

Of twenty-seven patients who had unilateral disease at the commencement of treatment, nineteen are alive and fit, two are unfit and six are dead apart from the one who was killed. Of forty-eight patients who had bilateral disease at the commencement of treatment, twenty-three are alive and fit, five are unfit and twenty are dead. Six patients had bilateral pneumothorax treatment and of these four are alive and fit and two are dead. Thus 70 per cent of unilateral cases benefited from collapse therapy, only two having required a thoracoplasty, whereas 48 per cent of bilateral cases benefited from collapse treatment, five of these patients having required a thoracoplasty.

Considering the differing clinical states of the patients at the start of their collapse therapy the final results are not surprising.

#### CONCLUSIONS

1. Very small transient pleural effusions arising during pneumothorax therapy are of no importance. Most effusions are due to the invasion of the allergic pleural cavity by the tubercle bacillus. These effusions are often the precursors

of tuberculous empyemata. They should be frequently examined both cytologically and bacteriologically; for these methods help to guide the physician in collapse therapy. More extensive use of them would possibly lower the incidence of empyemata and unexpandable lung.

2. Pleural effusions are associated with a high rate of abandoned pneumothoraces and consequently with a higher percentage of patients either unfit as a result of treatment or dead. This is not due to the pleural effusion or empyema which may arise from it but is due to advancing bilateral disease.

3. Tuberculous empyema, although a serious complication of pneumothorax treatment, can be controlled in most patients by aspiration of the pus and re-expansion of the lung. Thereafter, thoracoplasty is usually necessary.

4. The final figures for the successful results of pneumothorax treatment in this series tend to confirm the impression held in this Sanatorium for some time now, that in suitable unilateral cases there is a decided place for primary thoracoplasty. We cannot afford to allow 22 per cent of the patients with unilateral disease when admitted to the sanatorium to die because time is spent on ineffective pneumothorax therapy. Probably some of these patients could be saved by early thoracoplasty preceded by a short period of rest together with phrenic crush and pneumoperitoneum, where necessary.

#### CONCLUSIONES

##### *Pleuresía con Derrame durante la Neumotoracoterapia*

1. Los pequenísimos y pasajeros derrames pleurales que se presentan durante el neumotórax terapéutico no revisten importancia. La mayor parte de los derrames se deben a la invasión de la alérgica cavidad pleural por el bacilo tuberculoso y son a menudo los precursores de empiemas tuberculosos. Por esa razón deben ser estudiados con frecuencia tanto citológica como bacteriológicamente, pues esas técnicas orientan al médico en la colapsoterapia, y empleadas en mayor grado quizás rebajaran la incidencia de empiemas y de pulmones inexpandibles.

2. Los derrames pleurales van asociados a un elevado coeficiente de neumotóraces abandonados y por lo tanto a un porcentaje más alto de enfermos ya inhabilitados a consecuencia del tratamiento o muertos. Esto no se debe al derrame pleural o al empiema derivado del mismo sino a la enfermedad bilateral progresiva.

3. Aunque constituye una grave complicación de la colapsoterapia, puede cohibirse el empiema tuberculoso en la mayoría de los enfermos mediante la aspiración del pus y la re-expansión del pulmón, después de lo cual suele necesitarse la toracoplastia.

4. Las cifras definitivas de éxitos de la neumotoracoterapia en esta serie tienden a confirmar la impresión formada desde hace algún tiempo en el Sanatorio donde trabaja el A., al efecto de que en los casos unilaterales adecuados tiene su puesto la toracoplastia primaria. No puede dejarse morir a 22 por ciento de los enfermos unilaterales recibidos en dicho Sanatorio por malgastar el tiempo en una colapsoterapia ineficaz. Probablemente podrá salvarse a algunos de esos

enfermos mediante una toracoplastia temprana precedida de un breve período de descanso junto con trituración del frénico y neumoperitoneo, cuando resulte necesario.

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## AIR EMBOLUS IN PNEUMOPERITONEUM<sup>1,2</sup>

### Report of a Fatal Case

WM. H. BAILEY

Air embolus, through whatever route or in any quantity, may be a serious complication in an operation or a therapeutic procedure. The patient may recover after a brief but critical seizure, or he may have a sudden and tragic death within the space of a few minutes. The case to be reported here is one of the latter group. Within a matter of seconds from the time the patient first complained of feeling dizzy he had a convulsion of a few minutes' duration, followed by death thirteen minutes later.

The patient (*Mr. C. M. H.*) was admitted with a diagnosis of pulmonary tuberculosis. After admission to the hospital an additional diagnosis of endobronchial tuberculous involvement was made. Pneumoperitoneum was considered to be indicated because of the endobronchial disease and the extent of the bilateral involvement. The initial pneumoperitoneum was instituted October 12, 1946, with no untoward results. The first refill (in which the air embolus occurred) was done on October 24, 1946.

The account of the events observed by the physician who administered the air is most interesting and instructive and is recorded here in some detail.

"At 8:45 a.m., I started to give this patient a pneumoperitoneum refill. Using the previous site, this area was infiltrated with one-half per cent novocain. After complete infiltration, a blunt-edged, 19 gauge, two inch needle was inserted through the path of infiltration. After introducing this needle for a distance of about one and one-half inches, the resistance against the novocain infiltration was greatly diminished, thereby indicating that the point of the needle was in the peritoneal cavity. In attempting to withdraw the plunger of the syringe, this could not be accomplished, neither was any blood withdrawn during this procedure. Upon disconnecting the syringe, a drop of novocain was placed into the lug of the needle and this drop was aspirated intraperitoneally, again verifying the fact that the point of the needle was in the peritoneal cavity. The manometer tube was then connected to the needle and a fluctuation of zero plus one was obtained. Since this is a common reading in cases of pneumoperitoneum, the air valve was opened and the air permitted to enter the peritoneal cavity under gravity. This air flowed very freely and, at the end of the introduction of 100 cc. of air, the reading was still zero plus one. More air was then permitted to flow into the cavity, during which procedure the patient was asked several times if he felt any pain or untoward reactions. He stated that he felt fine and that he noticed no unusual sensations. Just when the 300 cc. mark was reached, the patient stated he was beginning to feel dizzy. The needle was therefore instantly withdrawn and the foot of the operating table elevated about twelve inches. About two seconds later, he began to thrash around in a general convulsion. He was given 1 cc. of adrenalin immediately. The patient by this time had lost consciousness but his respira-

<sup>1</sup> From the Clinical Laboratory of the Veterans Administration Hospital, Excelsior Springs, Missouri.

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tion and pulse continued. At this time he was given 2 cc. of adrenalin intravenously. Artificial respiration was given, oxygen was administered, and 5 cc. of coramine were given intravenously. Patient was still breathing and his heart sounds could be heard but his radial pulse could not be felt. About five minutes later he had a severe emesis which was cleared by suction. At this time the patient's heart beat and respiration stopped. The patient expired about fifteen minutes after the refill was started and thirteen minutes after the onset of dizziness began. About five minutes after the patient's death he was given 2 cc. of adrenalin intracardially but, despite all efforts to revive him, the patient expired."

### *Autopsy Findings*

On opening the chest a considerable number of very small air bubbles were seen in the mediastinal tissue over the trachea and the larger blood vessels above the heart.

*Lungs:* The right lung weighed 1,010 grams and the left lung 720 grams. Very strong pleural adhesions were present over the larger part of both lungs. On gross section, both lungs showed cavities of various sizes which were more numerous in the right lower lobe, and emphysema and hypostatic congestion.

*Heart:* The heart weighed 360 grams. Before removal of the heart, the large blood vessels were tied off outside the pericardium and sectioned above the ligatures. The heart and pericardium were removed *en masse* before being punctured. On gross section no air bubbles were discovered in the slightly increased pericardial fluid, although numerous small air bubbles were visible on the outer superior surface of the parietal pericardium. The pericardium was not opened under water, but no ballooning of pericardium before section could be discovered. On opening the heart cavities, a large quantity of frothy blood and stringy clot was found in the right auricle and ventricle; no air bubbles were found in the left side. The foramen ovale was firmly sealed. The valves were smooth and glistening. The heart walls were slightly thickened.

*Abdomen:* The abdominal muscles and subcutaneous fat were of normal thickness. The inner end of the pneumoperitoneal puncture wound was smooth and surrounded by a small bluish discolored area about 2 mm. in diameter. No hemorrhage or injury to the surface of any of the abdominal organs or tissues could be found. No abdominal adhesions were present. No tear or abnormality of the diaphragm could be discovered.

*Liver:* The liver weighed 2,460 grams and presented a slightly congested appearance with a smooth surface and regular outline. A normal degree of resistance was felt on cutting the liver and the cut surface was smooth and the markings normal. No air bubbles were found in liver tissue or vessels. No injury such as a tear or puncture wound of the surface of the liver was found.

*Spleen:* The spleen weighed 390 grams but, other than the increased size, presented a normal shape and appearance. On gross section the organ cut with a normal degree of resistance and the cut surface was moist and essentially normal.

*Kidneys:* The right kidney weighed 200 grams and the left, 220 grams. Both organs, were essentially normal in size, shape and appearance.

### *Microscopic Examination*

*Lungs:* Some portions of the lungs showed nearly complete consolidation by tuberculous reaction, necrosis with cavitation, giant cells, plasma cells, and marked peribronchial engorgements. Other portions showed less extensive involvement but contained many typical tubercles and giant cells.

*Heart clot:* Examination of the clot found in the heart showed irregular areas of leucocytes, erythrocytes and fibrin. No microscopic evidence that the clot had contained air bubbles could be elicited, although this finding was definite on gross examination.

*Liver:* The liver cells were somewhat granular but well stained. There was marked engorgement of all the blood vessels and a large vein in one area was nearly completely filled by a blood clot.

*Spleen and kidneys:* Marked engorgement of all the blood vessels was the principal reaction shown in these organs. The renal cells in many areas appeared granular and fragmented.

*Pathological diagnosis:* Pulmonary tuberculosis, chronic, with cavitation, bilateral, extensive. Air embolus, right heart, from pneumoperitoneum. Pneumomediastinum, slight. Chronic adhesive pleurisy. Marked congestion and granular degeneration of liver, spleen and kidneys.

#### DISCUSSION

Artificial pneumoperitoneum is not a rare therapeutic procedure. It was first instituted in the hope of relieving tuberculous enteritis (1) and has subsequently been used extensively in the treatment of pulmonary tuberculosis. Thus, pneumoperitoneum is no longer considered to be an experimental procedure. Simmonds (1), in London, reported 13,000 peritoneal air injections with 9 instances of air embolus and one death. Aslett and Jarman (2), also in England, reported 2 deaths in 42 patients treated with pneumoperitoneum, but stated that the majority of the patients were far advanced cases in which more complications could be expected to occur. Several series reported in this country and Canada compare favorably with the reports from England.

The potential dangers of pneumoperitoneum are well recognized. Fortunately, the frequency of serious complications is very low. Among the complications to be considered are: puncture of a hollow viscus, stomach or intestine; puncture of liver; direct entrance of needle into a vein; effusion of serum into the peritoneal cavity; mediastinal emphysema; and air embolus.

In the case presented above, slight mediastinal emphysema was noted but was not considered to have been a factor in the cause of death. The air presumably leaked slowly through some area in the diaphragm during the interval between the first and second air injections. It is stated by Aslett and Jarman (2) that such leakage may occur at the time the air is being introduced into the peritoneal space or some days later.

Air embolus is the complication of pneumoperitoneum that is most to be feared. Embolism is an ever present danger and should always be regarded seriously, even though only a small proportion of the cases prove fatal. Although the needle may be introduced properly and all precautions taken so as to feel sure that the needle point is free in the peritoneal cavity, air may still escape and enter the circulation through some undisclosed route.

The mechanics of the entrance of air into the venous circulation is a most fascinating question to attempt to answer. Unfortunately in the present case, as in many of the cases reported in the literature, the exact route of the air could



not be determined definitely. Thus only the possible routes for the entrance of air into the circulation can be discussed.

The possibility of the needle entering a fair sized vein and the air being injected directly into the venous circulation should never occur if proper care is taken. It may be possible, however, for a vein wall to be injured by the passage of the needle so that, when a sufficient pressure has been built up by the introduction of air, it may enter through the injured area. This possibility was not considered to be likely in the present case as no hemorrhage or injury inside the abdomen could be found. If the injured vein were in the abdominal wall, the air would have to leak back along the outside of the needle. This possibility is also unlikely in the present case for the air pressure in the abdominal cavity was not very great as the introduction of the air had just been started.

The needle could have failed to enter the abdominal cavity or, after entering, could inadvertently have been partially withdrawn and the air injected directly into the abdominal wall tissues. Such a course of events was believed to be unlikely in this case because the air was injected without any apparent resistance. Moreover, the pressure of zero to plus one reading on the manometer indicated that the needle was in the abdominal cavity when introduction of the air was started.

The air could have entered the liver or some other solid organ and thus gained entrance to the venous circulation from the tissues of the organ. It does not seem likely that this could have occurred as no puncture wound or injury to the liver or other organ could be found.

All writers are of the opinion that the amount of air which may produce a fatal embolus is extremely variable. A small quantity rapidly introduced can be quite as harmful as a large amount injected slowly. The symptoms of air embolism are so dramatic that the diagnosis is not too difficult in most cases. There is sudden shock, dyspnea, cyanosis, rapid weak pulse and often a peculiar heart sound which is difficult to describe. Convulsions may occur as a result of sudden anoxemia or a cerebral embolism. If cerebral embolism has happened, paralysis or blindness may occur in addition.

Batson (4) states that a free anastomosis between the veins of the abdomen and those of the vertebral venous plexus exists. These anastomoses are suggested as one possible route of cerebral air embolus in pneumoperitoneum. Although it was not thought that cerebral air embolism occurred in the present case, the patient's first symptom of dizziness, followed almost immediately by a convulsion, suggested that he either had a cerebral air embolus alone or in association with a cardiac air embolus. It is believed by Bard (5) that a rapidly induced anoxemia will result in unconsciousness, a convulsion, and collapse within forty-five to eighty-five seconds. A patient who has received such a severe shock as a cardiac air embolus of any appreciable amount might easily have described his unusual sensation as dizziness. It is also possible that the cardiac output had been sufficiently compromised to cause a sudden anemia of the cortical area of the brain, resulting in a convulsion.

Death caused by air embolism may be immediate or may occur after a few

hours. If the patient survives the first fifteen minutes, the prognosis is fairly good and rather rapid recovery over a period of a few days may reasonably be expected.

#### CONCLUSION

Artificial pneumoperitoneum has passed the experimental stage and should be considered a fairly safe procedure. All the technical details of injecting the air must be strictly followed. The injection of air should proceed very slowly at first. The patient should be watched very carefully and frequently asked if he experiences any unusual sensations. The injection of air should be stopped immediately if the patient becomes restless or complains of any unusual feelings.

#### SUMMARY

The clinical and postmortem findings of a case of cardiac air embolus after pneumoperitoneum refill are reported. The potential complications in the institution of pneumoperitoneum are reviewed and the principal symptoms of air embolus are listed. The possible routes for the entrance of air into the circulation during the introduction of air into the peritoneal cavity are discussed.

#### SUMARIO

##### *Acroembolia en el Neumoperitoneo*

Comunícase un caso de embolia gaseosa cardíaca letal que sobrevino durante una reinsuflación de neumoperitoneo, junto con los hallazgos autópsicos. Repásanse las complicaciones potenciales que entraña la ejecución del neumoperitoneo y enúmeranse los síntomas cardinales de la embolia gaseosa. También se discuten las posibles vías por las que puede pasar el aire a la circulación al introducirlo en la cavidad peritoneal.

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## FUNCTIONAL PULMONARY CHANGES FOLLOWING BRONCHOGRAPHY<sup>1</sup>

WILLIAM A. ZAVOD<sup>2</sup>

Since 1922, when Forrestier introduced lipiodol as a contrast medium for X-ray visualization of the bronchial tree, the bronchogram has become an important aid in the study of diseases of the bronchi. Bronchography to-day is a common procedure and is safe when the proper technique is employed. The oil, apparently, has no ill effect upon the bronchi or the pulmonary parenchyma.

Complications during or following bronchography arise occasionally. Most of them, however, can be avoided by ascertaining that the patient is not hypersensitive to cocaine or its derivatives; that he does not suffer from acute pulmonary disease, advanced emphysema, or other illness that contraindicates the procedure.

Having taken all precautions against complications, one is still faced with the fact that in many cases the lipiodol is retained in the lungs for many months. Subjectively the patient is not disturbed by the retained lipiodol. The question arises, however, as to whether there is any functional disturbance in the respiratory system that can be measured. Is there an immediate effect upon the respiratory function when the oil is still in the bronchi? What changes occur in the pulmonary function when the lipiodol is found in the alveoli a few days after the bronchogram? If changes do occur, how long do they persist? It was to answer these questions that the following study was undertaken.

The investigation was based upon a study of 50 unselected patients who had diagnostic bronchograms during their hospitalization.

### PLAN OF INVESTIGATION

Spirometric studies as described by Cournand, Richards and Darling (1) were carried out on every patient in the following manner. The patient was familiarized with the procedure and several trial tests were done until the patient learned to remain completely relaxed during the test. Spirometry was done every morning at the same hour for five consecutive days. From the tracings, the oxygen consumption per minute ( $O_2$ ), minute volume (MV), vital capacity (VC), ventilation equivalent (VE), respirations per minute (RPM), tidal air (TA), complementary air (CA) and reserve air (RA) were determined. Unfortunately, maximum breathing capacity determinations, which would have greatly enhanced the study, could not be done as the apparatus was not equipped for such determinations. The bronchogram was done on the sixth day. The technique used has been described in a previous report (2). All lobes of both lungs were outlined with 20 cc. of lipiodol instilled intratracheally through a catheter. The left lung received 9 cc. and the right lung 11 cc. Cases which showed in-

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complete filling were excluded. Each patient received 0.05 to 0.1 g. of nembutal one half hour prior to the bronchogram. Postural drainage was instituted for fifteen minutes after the procedure and bed-rest for forty-five minutes. Another spirometry was done immediately after the rest period and daily tests at the same hour until all data had reached prebronchogram levels on two successive days.

The purpose of the daily spirometric studies before the bronchogram was to establish a mean for the various values in each patient, so that it might serve as a standard to measure any deviation in those values after the bronchogram.

TABLE 1A

*Daily spirometric studies before bronchogram. Case 5 J.P.*

	O <sub>2</sub>	MV	VC	VE	CA	TA	RA	RPM	CA & TA
1st day	269	6,000	3,960	2.2	3,200	428	330	14	3,628
2nd day	285	7,300	3,890	2.5	3,150	460	330	16	3,610
3rd day	285	6,285	3,960	2.2	3,150	428	330	13	3,578
4th day	276	6,565	3,860	2.3	3,100	460	363	15	3,560
5th day	236	6,036	3,960	2.4	3,150	428	363	14	3,578

TABLE 1B

*Daily spirometric studies after bronchogram. Case 5 J.P.*

1st hr.	306	5,024	3,300	1.6	2,680	390	165	13	3,070
1st day	285	6,505	3,365	2.1	2,665	464	198	14	3,109
2nd day	276	7,161	3,960	2.4	3,120	477	330	15	3,597
3rd day	288	6,716	3,960	2.4	3,100	444	363	15	3,544
4th day	277	6,250	3,960	2.4	3,200	413	363	15	3,613

TABLE 1C

*Daily percentage loss of function after the bronchogram. Case 5 J.P.*

	VC	CA & TA	RA
1st hr.	16%	14%	52%
1st day	16%	14%	43%
2nd day	0	0	0
3rd day	0	0	0
4th day	0	0	0

## RESULTS

Tables 1A, 1B and 1C will serve as illustrations of the values obtained in a single patient before and after a bronchogram.

Analysis of table 1A shows a comparatively wide daily fluctuation for oxygen consumption and minute volume, while the vital capacity, complementary air, tidal air and reserve air are fairly constant. Furthermore, complementary air and tidal air are reciprocal and their sum gives a daily value that is still more constant.

The mean values for vital capacity, complementary air plus tidal air and reserve air in case 5, as determined from the data in table 1A, for the five-day period are 3,927, 3,586 and 343 cc. respectively, and are used for comparison with the data obtained after the bronchogram (table 1B). In table 1C may be seen the percentage loss of function following the bronchogram.

Table 1C shows that in case 5 the greatest loss was in reserve air (RA) and that forty-eight hours after the bronchogram all values returned to the prebronchogram level.

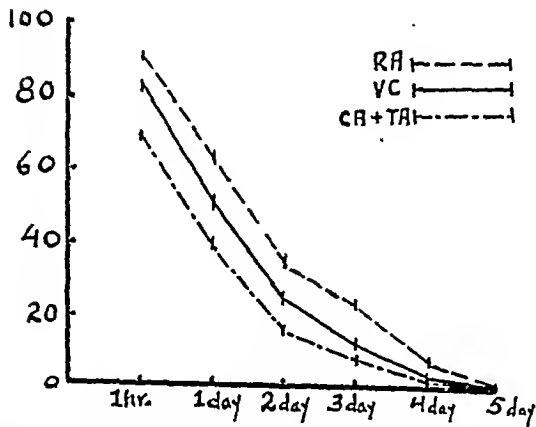
The mean values for vital capacity, complementary air plus tidal and reserve air during the prebronchogram period were thus determined for each case and compared with the values obtained each day in the postbronchogram studies. The results are expressed in graphs 1 and 2.

Analysis of graphs 1 and 2 shows that over 80 per cent of the patients had an appreciable loss of vital capacity and close to 100 per cent had a loss of reserve air one hour after the bronchogram. Only about 70 per cent of the patients showed a loss of complementary air plus tidal air. This can be explained by the circumstance that some of the cases had a loss chiefly in reserve air. A loss of 100 cc. of reserve air when the total reserve air in a particular case is only 400 cc. constitutes a loss of 25 per cent. The complementary air and tidal air may show no loss, and the 100 cc. lost will therefore show up in the vital capacity. This will be of little moment, namely, 2.5 per cent loss when the vital capacity is 4,000 cc.

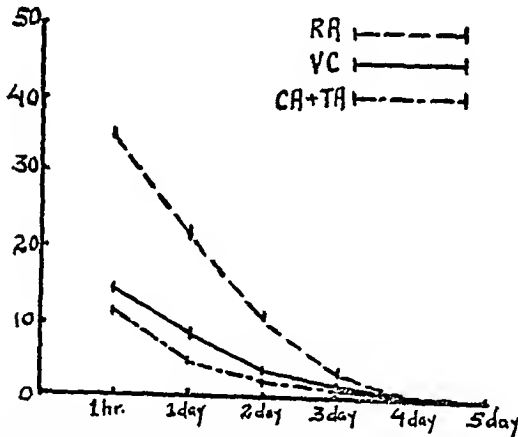
Graph 2 shows that the average percentage loss was highest for reserve air. It ranged from 0 in 5 cases to 83 per cent loss in one case, one hour after the bronchogram. The average loss for complementary air plus tidal air and vital capacity was 12 per cent and 15 per cent, respectively. Daily spirometry showed that all values returned to the prebronchogram level by the end of the fifth day.

The various diagnoses in the group of patients studied may be seen in table 2.

*Comment:* If the total capacity of the lungs is assumed to be 5 to 6 liters, it would not be anticipated that there would be any appreciable reduction in pulmonary function after the instillation of only 20 cc. of lipiodol. On the other hand, the anatomy of the lungs is such that simultaneous plugging of the smaller bronchi with viscous lipiodol could asphyxiate a person by cutting off the access of air to the aveoli. The reason this does not happen is readily found when the passage of the oil down the bronchial tree is observed under the fluoroscope. The patient is in the recumbent position on the fluoroscopic table and the oil can be seen running down the larger bronchi into the subdivisions. The progress of the oil downward is not a continuous flow. It is drawn forward by the inspiratory column of air and forced back during expiration. The walls of the bronchus that were initially in contact with the oil are now opaque, apparently coated with a layer of oil. The to and fro rocking process of the oil in the bronchi continues for the next few respirations and stops. It is possible that the oil actually plugs the smaller bronchi temporarily and is thus rocked by the air currents until the air breaks through the plug. The bronchus now has a layer of lipiodol on its walls instead of a plug.



GRAPH 1. Percentage of patients who showed loss of VC, CA + TA and RA



GRAPH 2. Average percentage loss of VC, CA + TA and RA in 50 patients

TABLE 2

*Clinical diagnosis in group of patients studied*

Chronic bronchitis	{ mild.....	13	Bronchial asthma { moderate.....	3
	{ moderate.....	2		3
	{ severe.....	4	Bronchiectasis.....	9
Emphysema	{ advanced.....	2	Ulcerative bronchitis (following gunshot wounds).....	1
	{ early.....	1	Interlobar effusion.....	1
Chronic lung abscess.....		2	Bronchogenic carcinoma.....	1
Post atypical pneumonia.....		4	Deformity of chest (congenital)....	1
Normal lungs.....		2	Congenitally small bronchi.....	1

This may also explain the marked reduction of reserve air after the bronchogram. The presence of a layer of oil on the walls of the smaller bronchi may reduce their lumina during forced expiration to a degree where considerable air may be trapped behind them.

Roentgenograms taken the day after a bronchogram show that the lipiodol has left the bronchi. Some of the oil has run out by postural drainage, some of it is coughed up, the remainder is found in the pulmonary lobules and appears as patchy granular infiltration. In some patients the lungs rid themselves of the oil within a few days; in others, residual oil may be seen many months after the bronchogram (thirteen months in one case of this series.) Five days after the bronchogram, all patients in the present series showed a complete return of the pulmonary function to the prebronchogram level.

Pathologic changes that were present in the lungs at the time of the study did not, apparently, interfere with their ability to regain their former functional capacity. Nine disease processes of the lungs are represented in this series; yet all patients returned to their original functional level within five days. Some showed more rapid regain of function than others. The slowest were the cases of emphysema and chronic bronchitis.

The fact that the average age of the patients studied was 28 (youngest 19, oldest 47) may have influenced the results. None had long standing pulmonary disease, none had extensive lung destruction or marked pulmonary fibrosis. The bronchiectases were limited to one lobe only, the patients with chronic bronchitis had acquired the disease comparatively recently. Most of the patients had moderately good pulmonary function.

#### SUMMARY

1. Fifty patients who had had diagnostic bronchograms were studied spirometrically before and after the bronchogram.
2. Ninety per cent of the patients showed loss of pulmonary function and decrease in some pulmonary volumina one hour after the bronchogram.
3. The highest average loss was in the reserve air.
4. Daily spirometric studies after the bronchogram revealed that the loss is recovered gradually and that return to the prebronchogram level occurs within a maximum of five days.

#### SUMARIO

##### *Alteraciones Postbroncográficas de la Función Pulmonar*

1. A 50 enfermos en quienes se habían obtenido broncografías de diagnóstico, se les estudió antes y después de las mismas.
2. Noventa por ciento de los pacientes revelaron pérdida de función pulmonar y disminución de algunos de los volúmenes pulmonares una hora después de la broncografía.
3. La mayor pérdida media correspondió al aire de reserva.

4. Los estudios espirométricos diarios realizados después de la broncografía revelaron que la pérdida se recupera paulatinamente y que el retorno a las cifras prebroncográficas tiene lugar en término de cinco días como máximo.

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#### *Acknowledgment*

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## INFECTION OF CHICK AND DUCK EMBRYOS WITH TUBERCLE BACILLI<sup>1</sup>

ARNOLD H. EGGERTH, EDITH DRESHER AND VIRGINIA C. McOSKER

### INTRODUCTION

The developing chick embryo has proved to be a valuable host in the study of experimental tuberculosis. Several procedures have been used for infecting the embryonated egg. The chorio-allantoic membrane has been exposed and the inoculum placed directly on the membrane (1, 2, 3, 4, 5, 6, 7), or injections have been made into the yolk sac (6, 7) or into a vein (7, 8).

In those studies in which the tubercle bacilli were implanted on the chorio-allantoic membrane, chick embryos of nine to twelve days of age have been most often used, as the mortality with younger embryos was found to be excessively high (2, 3, 7). As may be seen from the experimental data to be presented, the resistance of chick embryos to tuberculous infection increases sharply on and after the eighth and ninth days of incubation. Hence, when embryos of this age or older are employed, very large doses of tubercle bacilli are necessary to produce lesions. Various investigators (4, 9, 3, 5) have used inocula ranging between 0.01 and 5.0 mg. of tubercle bacilli for the production of lesions in chick embryos. Lee and Stavitsky (7) used an inoculum of  $\frac{1}{6}$  mg. of bacilli for infection of the chorio-allantoic membrane and Dubos and his associates (6) found 0.001 mg. to be the minimal infecting dose for this purpose. As 1.0 mg. of moist culture of tubercle bacilli contains approximately  $10^9$  (one billion) living organisms (10), the inocula used by these various investigators contained from one million to five billion living tubercle bacilli.

It is the purpose of the present paper to report the production of numerous tubercles in chick membranes with doses as small as  $10^{-6}$  to  $10^{-7}$  mg. of bacilli (approximately 1,000 to 100 organisms); and, in the case of duck embryos, occasional lesions with an inoculum of  $10^{-8}$  mg., or 10 organisms.

### METHODS

The tubercle bacilli used were chiefly human type strains recently isolated. Experiments were also done with the avirulent strains R1 and BCG. One human type strain (N) has been passed through chick embryos for 15 passages, to determine the effect of such passage on virulence for the chick.

Cultures were grown on slants of Bordet-Gengou medium to which 3 per cent of glycerol and 15 per cent of rabbit serum had been added. Two-week cultures were ground in a Ten Brock tissue grinder with broth, then centrifugated for ten minutes at 1,000 r.p.m. Examination of the supernatant fluids showed mostly single bacilli, with few small clumps. The suspensions were then diluted to give a turbidity equal to that of tube No. 3 of the McFarland standards

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(0.3 ml. of 1 per cent barium chloride plus 9.7 ml. of 1 per cent sulfuric acid). Such a suspension contains approximately one billion organisms per ml., or 1.0 mg. of moist culture per ml. Colony counts were made in every experiment.

The eggs used were those of white Leghorn chickens and of Pekin ducks.

Repeated experiments showed that the lesions of the chorio-allantoic membrane are exactly the same in extent and in their histopathology, whether the inocula are placed on top of the membrane through a window in the shell or injected into the allantoic cavity. (As the allantois is not a large sac until after the fourth day of incubation, embryos younger than five days must be inoculated on the membrane.) Embryos suffer less trauma when the inoculation is made into the allantoic sac, and the survival of chicks is much better when this method is employed. Hence, most of the inoculations of the chorio-allantoic membrane were made in this manner.

In a number of experiments, inoculations were made into the amniotic sac, employing a technique slightly modified from that described by Beveridge and Burnet (11). Yolk sac injections were made in the usual way (12).

After incubation of the infected eggs (for nineteen or twenty days for the chick eggs, or twenty-six or twenty-seven days for duck eggs), the membranes were removed and immersed in 1 per cent phenol for twenty-four hours. Whenever the number of tubercles on a membrane was small, smears were made from the suspected lesions and stained, to exclude nonspecific ulcers which sometimes occur, as reported by Beveridge and Burnet (11). Material for sections was fixed immediately in Zenker's fluid.

## RESULTS

*The effect of the age of the embryo on the chorio-allantoic lesions:* In table 1 and figure 1, data are presented which indicate that the resistance of the chorio-allantoic membrane to infection with tubercle bacilli varies considerably with the age of the embryo at the time of inoculation. The membranes were most susceptible to infection on the sixth and seventh days of incubation. Embryos of three, four and five days' development were slightly less susceptible to inocula of  $10^{-6}$  mg., and failed to show any lesions with  $10^{-7}$  mg., in contrast to embryos aged six to eight days. On the ninth day of incubation, resistance to infection is already considerably greater than on the eighth day. On the tenth to twelfth days, only large doses ( $10^{-4}$  mg. or more) will produce tubercles on the chorio-allantoic membrane, and these are generally few in number.

*The effect of chick passage on the virulence of tubercle bacilli for the chick:* Only one strain of tubercle bacilli (N, human type) was passed through a series of chick embryos. The progressive increase in the virulence of this strain for the chick embryo may be seen in table 2. Before chick passage, tubercles appeared uniformly in embryos of eight days or less which had been inoculated with  $10^{-4}$  mg. of bacilli. Inoculation of the membranes with  $10^{-5}$  and  $10^{-6}$  mg. of organisms resulted in lesions in 70 and 40 per cent, respectively. Tubercles were not produced by inoculation of  $10^{-7}$  mg. of bacilli.

In contrast, after 9 chick passages, lesions developed in all eggs inoculated with  $10^{-5}$  mg. of bacilli; in 82 per cent of the eggs which received  $10^{-6}$  mg.; and in 70 per cent of the eggs inoculated with  $10^{-7}$  mg. of organisms. No macroscopic lesions were produced in chick eggs by an inoculum of  $10^{-8}$  mg., though the bacilli were living and multiplying, as shown by the fact that they usually could be cultured from bits of such membranes.

In tables 1 and 2, the results are tabulated simply as positive or negative, irrespective of whether the numbers of tubercles were many or few. In table 3 may be seen the approximate numbers of tubercles observed with different infecting dosages. It may be noted that, as the virulence of the tubercle bacilli was increased by chick passage, both the minimal infecting dose and the number of tubercles on the membranes were affected.

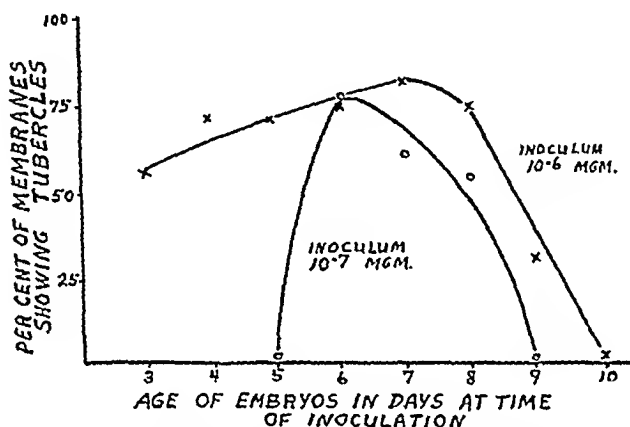


FIG. 1. The incidence of tubercles on the chorio-allantoic membranes of chick embryos inoculated with  $10^{-6}$  and  $10^{-7}$  mg. of tubercle bacilli, strain N, which had been passed through chick embryos. All inoculations were made into allantoic sacs or on chorio-allantoic membranes of embryos three to eight days old.

*Infection of the chorio-allantoic membranes of duck embryos:* As the incubation period of duck eggs is four weeks instead of three, it was thought that the extra week would allow a greater development of lesions in duck eggs. Several batches of duck eggs were inoculated with the N strain of tubercle bacillus (which at that time had been passed 8 to 10 times through chick embryos). It was found that:

(a) Nine- to eleven-day duck embryos were most favorable for producing lesions; younger (six-day) embryos were less easily infected by small doses.

(b) The lesions on the chorio-allantoic membrane were thicker, denser, and more hemorrhagic than those of chick embryos. Ectodermal buds and trabeculae were even more conspicuous in sections than they were in chick embryos. Otherwise the histological picture was the same, as was true also of the lesions in the liver and spleen.

(c) Tubercles regularly appeared on the chorio-allantoic membrane with inocula of  $10^{-6}$  and  $10^{-7}$  mg. of culture (intraallantoic inoculation in nine- to

TABLE 1

*Number of embryos showing tubercles on the chorio-allantoic membrane*

CULTURE	AGE OF EMBRYO	MG. OF TUBERCLE BACILLI INOCULATED							
		10 <sup>-4</sup>		10 <sup>-5</sup>		10 <sup>-6</sup>		10 <sup>-7</sup>	
		Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
	<i>days</i>								
N	7	15	0	7	3	6	2	0	8
N	8	6	0	5	2	2	11	0	4
N	9			8	3	1	8		
F	8	6	0	6	0	3	5	0	5
S	8	3	0	4	1	2	2	0	4
AJ	8	2	0	4	0	2	4	0	4
N (C. P.)*	3	4	0	8	1	11	9	0	9
N (C. P.)*	4	2	0	6	1	11	4	0	4
N (C. P.)*	5	3	0	9	0	8	3	0	5
N (C. P.)*	6	4	0	8	0	27	9	14	4
N (C. P.)*	7	8	0	24	2	31	6	10	6
N (C. P.)*	8	4	0	8	0	18	6	8	6
N (C. P.)*	9	4	0	9	1	5	11	0	7
N (C. P.)*	10	4	0	0	6	0	6	0	6
N (C. P.)*	11	2	1	0	5	0	4	0	4
N (C. P.)*	12	3	0	0	6	0	7	0	4

\* N (C. P.) = Strain N, passed through chick embryos. The number of passages varied from 2 to 15 in different experiments. All inoculations made into allantoic cavity or on chorio-allantoic membrane.

TABLE 2

*The effect of chick passage on the minimal infecting dose. Number of embryos showing tubercles on the chorio-allantoic membrane*

NUMBER OF CHICK PASSAGES	MG. OF TUBERCLE BACILLI INOCULATED*							
	10 <sup>-4</sup>		10 <sup>-5</sup>		10 <sup>-6</sup>		10 <sup>-7</sup>	
	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
0	21	0	12	5	8	13	0	12
2	3	0	14	3	21	14	0	7
3	2	0	5	0	6	3	0	6
6	3	0	4	0	4	2		
7	4	0	6	0	4	3	0	5
8	4	0	12	1	20	4	2	4
9			5	0	16	5	2	2
10			2	0	3	0	2	0
11	5	0	9	0	7	3	5	5
12	4	0	3	0	6	0	6	0
13			3	0	2	0		
14					12	3	11	5
15					6	0	4	0

\* N strain of tubercle bacillus used. All inoculations into allantoic sac or on chorio-allantoic membrane. All embryos three to eight days old at time of inoculation.

eleven-day embryos); 3 out of 12 eggs receiving  $10^{-8}$  mg. developed two to eight tubercles each (confirmed by smear).

*Inoculations into the amniotic cavity:* When tubercle bacilli were inoculated into the amniotic cavity of nine-day chick embryos, doses of  $10^{-4}$  mg. or more produced tubercles. The lesions usually did not appear on the amnio-allantoic membrane, but on the back of the allantoic sac where it extends over the yolk. Sections showed numerous tubercles in the wall of the allantoic duct. In a few cases, tubercles were also found on the chorio-allantoic membrane. Lesions in the spleen and liver were no more extensive, and no different histologically, from those produced by intraallantoic inoculation.

TABLE 3

*The approximate number of tubercles on the chorio-allantoic membranes before and after chick embryo passage*

CULTURE	INOCULUM*	NUMBER OF TUBERCLES				
		100 or more	20 to 100	5 to 20	1 to 5	0
N strain before chick embryo passage	mg.					
	$10^{-4}$	18	2	1	0	0
	$10^{-5}$	6	4	1	1	5
	$10^{-6}$	0	3	2	3	13
	$10^{-7}$	0	0	0	0	12
N strain after 2 to 8 chick embryo passages	$10^{-4}$	12	4	0	0	0
	$10^{-5}$	22	9	9	1	4
	$10^{-6}$	1	11	20	23	26
	$10^{-7}$	0	0	1	1	22
N strain after 9 to 15 chick embryo passages	$10^{-4}$	9	0	0	0	0
	$10^{-5}$	11	5	3	3	0
	$10^{-6}$	20	16	6	10	11
	$10^{-7}$	0	10	15	5	12

\* All inoculations made into allantoic sac or on chorio-allantoic membranes of embryos three to eight days old.

The inoculation of ten-day-old duck embryos by this route with  $10^{-7}$  mg. or more of culture produced numerous tubercles. The lesions occurred chiefly on the back of the allantois near its fusion with the amnion. Tubercles also appeared on the amnio-allantoic membrane and occasionally on the chorio-allantoic membrane.

*Inoculations into the yolk sac:* Very small inocula of tubercle bacilli will grow extensively in the yolk sacs of embryonated eggs (6). They will, however, grow equally well in the yolks of nonfertile (grocery store) eggs. In the present investigation it was found that excellent growth appeared in sixteen days in the yolks of nonfertile eggs inoculated with  $10^{-8}$  mg. of bacilli, *provided that the inoculated eggs were shaken vigorously every few days to distribute the tubercle bacilli.*

Inocula of less than  $10^{-3}$  mg. into the yolk sac of six-day embryos did not produce tubercles on the chorio-allantoic membrane. With inocula of  $10^{-3}$  mg. or more, tubercles were often, though not always, observed at that site. As the six-day embryo is highly susceptible to infection by way of the allantoic sac, it is very probable that the tubercles on the chorio-allantoic membrane were due to the variable number of organisms introduced into the allantoic cavity in making the yolk sac inoculations.

#### DISCUSSION

From the above data it may be seen that the age of the embryo at the time of inoculation is of primary importance when the dose of tubercle bacilli is small. Chick embryos are most susceptible to chorio-allantoic infection when six to seven days old; the corresponding age in duck embryos is ten days. Younger embryos are less susceptible to very small doses. After the eighth day of embryonic life, the resistance to tuberculous infection increases greatly. When the chick embryo is used in chemotherapeutic or serotherapeutic studies, this fact must be taken into consideration.

Beveridge and Burnet point out in their monograph (11) that, for many viruses and rickettsiae, the age of the embryo is a critical factor in infection. For example, rabies virus infects chick embryos only when they are less than eight days old. Other viruses (fowl pox, canary pox, herpes, vesicular stomatitis, vaccinia, ectromelia) were usually more infectious for embryos younger than nine days than for those that were older. These authors state that "degenerative and necrotic changes occur more readily in the membranes of younger embryos, and retrogression of lesions with complete repair is less commonly seen." In the experience of the present investigators chick embryos of less than eight days in age are more readily infected with hemolytic streptococci than older embryos.

Moore (3), Emmart and Smith (2, 4) and Fite and Olson (5) have considered the relationship of virulence of tubercle bacilli (as measured by guinea pig virulence) to their ability to produce lesions on the chorio-allantoic membrane. Moore, and Emmart and Smith conclude that infectivity for the chorio-allantoic membrane is an index of such virulence, whereas Fite and Olson reject this conclusion. The latter investigators were struck by the fact that the R1 strain, which is avirulent for the guinea pig, nevertheless produced lesions as extensive as those caused by highly virulent strains in the doses employed (1.0 and 0.01 mg. of culture in nine-day embryos).

In the present study, using seven- and eight-day embryos, each of 4 recently isolated human type strains produced extensive lesions with inocula of  $10^{-4}$  mg. of bacilli. Moreover, approximately two-thirds of the embryos were successfully infected with  $10^{-5}$  mg. of bacilli, and inoculation with  $10^{-6}$  mg. of culture infected about one-third (table 1). In contrast, the R1 strain in seven-day embryos never produced tubercles with an inoculum of  $10^{-4}$  mg. and produced lesions in only one-half of the embryos infected with a dose of  $10^{-3}$  mg. Inoculation of  $10^{-2}$  and  $10^{-1}$  mg. of R1 produced lesions as described by Fite and Olson. The strain BCG produced numerous small tubercles with inocula of 1.0 mg.,

though smaller doses were without effect. Thus, by using younger embryos and suitably smaller doses, differences in virulence can be clearly demonstrated among these strains. These differences are obscured when large infecting doses and older embryos are used.

Chick passage enhanced the virulence of the N strain of *M. tuberculosis* for the chick embryo. This was shown by a reduction in the minimal infecting dose (from  $10^{-6}$  to  $10^{-7}$  mg.) and, even more strikingly, by the extent of the lesions when larger doses were employed. To obtain heavy confluent lesions with cultures before chick passage, doses of  $10^{-1}$  to 1.0 mg. of organisms must be employed. After a number of chick passages, doses of  $10^{-3}$  to  $10^{-2}$  mg. produce an enormously thickened (3 to 4 mm.) tuberculous area on the chorio-allantoic membrane.

In spite of the longer incubation period, duck embryos were not appreciably more sensitive to chorio-allantoic infection than chick embryos. When inoculated into the amniotic sac, however, the duck embryo was more sensitive than the chick, as the minimal infecting doses were  $10^{-7}$  and  $10^{-4}$  mg. of bacilli, respectively.

#### SUMMARY AND CONCLUSIONS

1. The chick embryo of six to eight days of age is most susceptible to infection with tubercle bacilli. Older embryos are much more resistant.
2. Chick passage of one strain of *M. tuberculosis* increased its virulence for the chick embryo.
3. The duck embryo has no advantage over the chick embryo except when the inoculation is made into the amniotic cavity.

#### SUMARIO Y CONCLUSIONES

##### *Infección de los Embriones de Pollo y Pato con Bacilos Tuberculosos*

1. El embrión de pollo es más susceptible a la infección con bacilos tuberculosos a la edad de 6 a 8 días. A una edad mayor es mucho más resistente.
2. El pase por el pollo de una cepa de bacilo tuberculoso acrecentó su virulencia para el embrión de pollo.
3. El embrión de pato no muestra ventaja alguna sobre el embrión de pollo, salvo cuando se hace la inoculación en la cavidad amniótica.

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## SPUTUM EXAMINATION<sup>1,2</sup>

A Comparative Study of the Clorox and Tergitol-Javelle Water Concentration Methods

PHILIP SCHAIN, SAM MAGDALIN AND ANTHONY RUSSO

Another (1) review of certain sputum concentration methods (2, 3, 4) for the demonstration of tubercle bacilli has been made to determine whether any of them were superior to the Tergitol-Javelle Water technique, originated in 1938 at Sea View Hospital and since adopted by a number of other institutions and health departments. The principal features sought in a concentration method are maximum recovery of organisms, ease of operation, and speed of performance. As it appeared that these features were most satisfactorily combined in the Clorox method, a direct comparison was made between this and the Tergitol Javelle Water technique.

### MATERIALS

Clorox samples from four different sources were pooled and used as the representative reagent.

Tergitol-Javelle Water was made by mixing equal amounts of Tergitol OS<sup>3</sup> (hospital grade) and Javelle Water, using only enough of each to last for not more than two days. The Javelle Water was prepared by adding 400 g. of fresh chlorinated lime (30 per cent available chlorine) to 600 g. of anhydrous sodium carbonate dissolved in 4,000 cc. of distilled water. The combination was mixed vigorously for several minutes and the mixing repeated three times thereafter at hourly intervals, after which it was allowed to settle overnight. The supernatant fluid was then filtered into a brown bottle containing enough chlorinated lime to cover the bottom. The bottle was shaken and tightly stoppered. This procedure serves to prevent deterioration of the product, which contains between 2.5 and 4.0 per cent sodium hypochlorite and is stable for a period of at least a month, especially if kept below room temperature. If cloudy, the reagent must be filtered before use.

Stain was made by dissolving 8 g. of crystalline basic fuchsin (Harleco brand) in 1,000 cc. of 5 per cent phenol previously heated to 60°C. Twice daily, before the first and after the final use, the stain was heated to 60°C. and filtered hot through a medium grade of paper. The dye can be reused for a period of at least a week, or more, depending upon the number of slides stained. When precipitation is seen on the stained slides, new fuchsin solution is indicated.

### PROCEDURE

Two hundred specimens, collected only from patients whose direct sputum examinations had been negative on at least three previous monthly examinations, were included in this series. Each specimen was carefully mixed, to avoid mechanical digestion, and divided into two portions so that each contained compar-

<sup>1</sup> From the Laboratory Services of the Veterans Administration Hospital and Sea View Hospital, Staten Island, New York, New York.

<sup>2</sup> Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

<sup>3</sup> Tergitol OS (hospital grade) may be obtained at E. Machlett & Son, 220 East 23rd Street, New York, New York.

atively equal amounts of watery and purulent material. The volume was adjusted so that approximately ten cc. were present in each of the widemouth tubes or bottles used.

Clorox was added in approximately equal amounts to one portion of sputum, shaken three times during a two minute period and kept at room temperature for ten minutes. The *mixture* was then centrifuged at 3,000 r.p.m. for ten minutes in a 50 cc. tube. The supernatant fluid was discarded and the tube drained for two minutes. With an applicator, a small drop of sediment was transferred to one end of a slide and allowed to dry without fixing.

Tergitol-Javelle Water was added in approximately equal amounts to the other portion of sputum. The specimen was then either shaken as in the Clorox method, simply rotated for half a minute, or mixed with an applicator and then kept at room temperature for ten minutes. The method of mixing depended upon the type of specimen used and speed of reaction desired. The *clear solution* was then centrifuged at 3,000 r.p.m. for ten minutes in a 50 cc. tube, the supernatant fluid discarded, and the tube drained for at least five minutes to prevent dilution of the sediment with reagent. With an applicator, small swab or platinum spade, the sediment was scraped from the bottom of the tube, transferred to one end of a slide and allowed to dry with or without fixing.

Staining of the slides from both concentration methods was done by the non-alcoholic fuchsin method. Slides were inserted into a Petroff slide holder<sup>4</sup> and then placed into a monel metal or glass container of stain, previously heated to a temperature of 55° C. The slides were allowed to remain in the stain until the temperature had dropped to approximately 20° C. to allow for complete precipitation of the dye in the body of the organism. Normally the period of time necessary would be from ten to fifteen minutes, but on hot days this period had to be extended, and this was best done by removing the holder and slides from the container of stain after ten minutes and exposing them to the air until they were cool to the touch. The slides were then rinsed well in running water and placed in two changes of a solution of 2.5 per cent by volume of concentrated nitric acid in 95 per cent ethyl alcohol for about thirty seconds each, or until only a faint pink color remained. They were then rinsed in water, immersed for a few seconds in one per cent aqueous brilliant green containing 1 to 10,000 sodium hydroxide, again rinsed in water and dried.

#### RESULTS

Tubercle bacilli were demonstrable in 35 per cent of the slides prepared by the Tergitol-Javelle technique and in 27 per cent of the slides prepared by the Clorox method.

In specimens which contained relatively few bacilli, only one-half to one-third the time was required to establish their presence by the Tergitol-Javelle Water method as was required for Clorox. This resulted, in part, from the fact that Clorox clumps organisms and adversely affects their ability to retain fuchsin so

<sup>4</sup> Petroff slide holders may be obtained at E. Machlett & Son, 220 East 23rd Street, New York, New York.

that the bacteria are unevenly distributed and poorly stained; and, in part, from the inferior solvent property of Clorox as compared with Tergitol-Javelle Water.

#### DISCUSSION

Clorox does not completely digest sputa, as evidenced by the cloudiness of the fluid before and after centrifugation and by the comparatively large sediment obtained. In contrast, Tergitol-Javelle Water digestion usually results in a clear fluid (where there is no admixture of foodstuffs) which contains a very small sediment which must be scraped from the bottom of the tube. In this respect, it should be emphasized that a gross excess of reagent should not be used, as solution may be so complete that the sediment may be macroscopically invisible. In such instances, if the fluid contains no bacilli, the stained slide will be blank. Equal quantities of reagent and specimen should be used for the average specimen but, for watery samples, only one-third the quantity of reagent may be sufficient to cause solution. With very purulent specimens, as much as four times the average amount may be necessary. When a sputum is treated with an insufficient quantity of reagent, a clear product may be formed but, because of incomplete digestion, it may be gelatinous in character and result in a stringy, unsatisfactory sediment instead of a smooth, creamy one. To avoid this, it is recommended that, until experience is gained, all treated specimens be allowed to stand at room temperature for ten minutes, with an additional shaking if necessary, to take full advantage of the reagent's solvent property.

Examination of the stained slides clearly showed the superiority of Tergitol-Javelle Water over Clorox. In the former, the acid-fast bacilli were evenly distributed and appeared as plump brilliantly stained rods; when digested by the latter method, the organisms were found scattered in clumps and were thin, pale and unevenly stained. These same differences were noted when the staining was done by the alcoholic Ziehl-Neelsen method, except that the picture was poorer.

The nonalcoholic staining procedure was based on observations which showed that basic fuchsin in 5 per cent phenol, without alcohol, is soluble at temperatures around 55° C., and will precipitate at temperatures around 37° C. Precipitation occurs, not only in the container, but apparently also in and around the bacilli, resulting in larger, more solid and more deeply staining rods.

The question of the possible occurrence of false positives in such a mass staining method repeatedly arises and checks have been made on numerous occasions. False positives have not occurred in experimental tests and, to the writers' knowledge, have not been found in institutions using this method. The possibility cannot be ignored, however; and, where it is seriously considered, the use of equipment recommended by Steenken (5) may be used in conjunction with the above technique.

Attempts have been made to use the sediments concentrated either by Clorox or by Tergitol-Javelle Water as inocula for cultures. Thus far, efforts to neutralize the sediment properly, with the hope of rejuvenating the organisms for culturing, have proven unsatisfactory.

## SUMMARY

Examination of 200 specimens of sputum, which had been negative by direct smear on at least three examinations, revealed acid-fast bacilli in 35 per cent of those treated with the Tergitol-Javelle Water reagent and in 27 per cent of those prepared with Clorox.

The time required for a satisfactory microscopic examination when using the Tergitol-Javelle Water method was approximately one-half to one-third that required with the use of Clorox.

The superiority of Tergitol-Javelle Water resulted from the greater degree of sputum solution with consequent concentration of organisms, the even distribution of bacilli in the sediment, and the fact that the reagent does not alter the capacity of acid-fast organisms to retain the fuchsin stain.

## SUMARIO

*Examen del Esputo: Estudio Comparado de las Técnicas de Concentración con Clorox y con Tervitol-Agua de Javelle*

El examen de 200 esputos, que habían resultado negativos en frotos directos, por lo menos en tres exámenes, reveló 35 por ciento de positivos con el reactivo de Tergitol-Agua de Javelle y 27 por ciento al emplear Clorox.

El tiempo exigido para un examen microscópico satisfactorio con la técnica de Tergitol-Agua de Javelle fué aproximadamente de la mitad a la tercera parte que el exigido con el Clorox.

La superioridad del Tergitol-Agua de Javelle se debió a la mayor disolución del esputo con la consiguiente concentración de gérmenes, a la distribución uniforme de los bacilos en el sedimento y al hecho de que el reactivo no altera la capacidad de los microbios ácidosresistentes para retener el colorante de fuchsina.

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## "SPEED OF REACTION" HYPOTHESIS

### III. Current Epidemiological Questions in *re* Tubercle<sup>1</sup>

HIBBERT WINSLOW HILL<sup>2</sup>

He who ventures an hypothesis, i.e., a serious attempt to correlate observed facts and draw conclusions from them, should present the postulated correlations categorically in order to bring out in detail their consonances with the facts. The more numerous such actual consonances and the fewer the apparent incompatibilities, the more will the hypothesis merit consideration and minute analysis in order that its degree of adequacy may be assayed.

#### BRIEF REVIEW OF THE HYPOTHESIS

Tubercle in the human has long presented as its basic puzzle the question: Why, of many persons infected, do a majority show little or no material damage; relatively few show material damage; and still fewer die (1)?

The same question recurs concerning almost all the other infectious diseases and the writer's hypothesis offers the same explanation, *mutatis mutandis*, for all. It is postulated that the above listed varieties of outcome which a given specific natural infection may yield do not correlate directly, either with variations in the size of the initial dose of the infection, or with variations in the absolute amounts of the specific immunities which the respective infections may induce from the host's body tissues. The varieties of outcome do correlate, primarily and chiefly, with *variations in the promptness* (18, 19) with which those respective specific immunities may appear in nature (or by artifice) upon the scene of action, and so may begin to check the particular specific infection concerned.

The particular degree of such promptness which a particular host may show in relation to a specific infection is held to be due to a particular and very specific genetic item of his heredity (2). This genetic item is possessed at birth and, on infection, shows as a short or a long, or an intermediate, specific immunity time-lag; that is, the time-interval between a specific *immunogenic* stimulus and the resulting specific *immunity* response.

In nature, all persons (or animals) are capable of responding with a specific immunity to the specific immunity-eliciting stimulus of many different infecting pathogens, *e.g.*, most, if not all, persons may so respond to infections of smallpox, measles, diphtheria, typhoid, et cetera, with a corresponding form of immunity. Broadly speaking, no one form of immunity is of value against any pathogen other than that pathogen which elicited the immunity. Hence, every such person carries hereditary potentialities for making a whole battery of such specific immunities, which potentialities, however, lie wholly dormant until one or more are elicited by the corresponding pathogen or the immunity-eliciting products of that pathogen.

The genetically set length of these respective time-lags is held to be unalterable by any known environmental factor which the individual may encounter during his life. (Certain apparent instances of alterability of inherent time-lag length by environmental factors are discussed and reconciled later.)

This hypothesis stems from the long recognized fact that a definite *time-lag* always

<sup>1</sup> See General Summary by Dr. Haven Emerson at end of this paper.

<sup>2</sup> Died May 23, 1947, at Hackensack, Minnesota.

occurs between the date of any specific infection and the date of the appearance of the specific immunity which that infection induces from the body tissues.

Evidently, if there were no such time-lag, i.e., if any given specific infection and the specific immunity for it should appear in the tissues *simultaneously*, no infection could gain headway enough to produce damage.

Hence this hypothesis offers that all the evidence now available points to the view that specific infection and its chief opponent, specific immunity, conduct their interrelationships *as if* the primary and chief controlling factor influencing the outcome of such infection were the particular length of this time-lag. The length of the time-lag necessarily depends upon the particular speed with which a particular infected person may be genetically able to react in his attempts to produce specific immunity soon enough to check the otherwise rapidly increasing numbers of the infecting germs.

Obviously, the more rapid his speed of reaction, the shorter his resulting time-lag, and the greater his success in minimizing the damage of the infecting organisms.

Specifically applied to human infections with living virulent *Mycobacterium tuberculosis v. hominis*, it is visualized that the varied outcomes of such tubercle infections in nature develop *as if* the variations in outcome were primarily controlled by the respective speeds with which the respective hosts produce immunity in response to the immunity-eliciting stimuli of their respective tubercle infections.

Therefore, the large (75 per cent?) majority of the total infected population who are genetically fortunate enough to be able to make specific tubercle immunity fast will bring such immunity to bear on the infection early, while the bacilli are still relatively few. Thus, these few bacilli are checked promptly and with a relatively small amount of immunity before they can achieve material damage.

#### NATURAL INFECTION AND NATURALLY RESULTING SPECIFIC IMMUNITY ILLUSTRATED

A close parallel to the above concept may be seen in the functioning of the water-sprinkler system for combating a fire in a building.

The initial fire blaze resembles an initial dose of infection with an immunity-eliciting, pathogenic microorganism; as it is the initial blaze itself which stirs into action the hitherto inert water-sprinkler to furnish the fire-subduing water.

Note that the true efficacy, both of the sprinkler and of the immunity mechanism, does not consist in preventing respectively the initial blaze of fire or the initial dose of infection. Indeed, each of these initial invasions is respectively essential to the elicitation of the antidotal functions peculiar to each mechanism. The true objective of each mechanism is the limitation of the damage which the essential invasion otherwise may achieve in both instances. Consequently, the degree of success in such limitation is dependent in both instances on how soon or how late the respective mechanisms go into action.

Thus, if the water be released early by the initial blaze while the blaze is as yet relatively small, a relatively small amount of water will be wholly sufficient to extinguish the fire. But the longer the sprinkler is delayed in its response, the more will the fire gain headway, the greater will be the fire damage, and the larger will be the quantity of water required ultimately to subdue the resulting conflagration. Should the delay be too long, even huge amounts of water may prove inadequate; the whole building, sprinkler system and all, may be destroyed.

Just so is it, this hypothesis offers, with all the infectious diseases. The natural outcomes of infection vary, not with the quality or the ultimate quantity of the specific immunity evoked, but with the particular speed with which the host may respond with the required specific immunity to the demands for such immunity evoked by the infection itself.

*"Artificial" preinfection immunization:* "Artificial" preinfection specific immunity is secured by technical artifices which parallel somewhat the precautionary "turning on" of the sprinklers of a room not yet invaded by the fire. In effect, a well controlled "artificial" blaze is applied to the sprinkler-starting device, thus wetting down this room in advance so that the fire will not get a foothold at all.

*Post-morbid immunity:* If a water-sprinkler system subdues a fire and uses a considerable excess of water in so doing—leaving a surplus of water beyond the amount actually necessary to extinguish the fire—the surplus water will so wet down the building as to render it noninflammable for a time, i.e., until the building becomes dry again.

Just so, in parallel, the "concurrent" immunity necessary to quell an infection and result in recovery is produced in such excess of actual requirements that the unused surplus ("free immunity") (2) constitutes the post-morbid immunity which, until it fades out completely, protects against new cognate infections.

*Evidence from preinfection immunity:* The illustration outlined above is only an illustration of the hypothesis, not evidence of its validity.

But the phenomena of "artificial" preinfection and of postinfection immunity do furnish real evidence, in that these phenomena proceed as if they were in fact controlled, primarily and chiefly, by various time-lags.

All the infectious diseases for which "artificial" immunity is available furnish such evidence; but smallpox offers it in very direct and simple form. It is universally known that practically every person naturally infected with smallpox for the first time will develop the disease, yet the majority will ultimately recover. The recovered individuals show thereafter a degree of persistent specific immunity against further successful invasion by smallpox.

In other words, the phenomena of smallpox indicate that most persons possess inherent potentialities for the production (on smallpox infection) of specific immunity to smallpox on a huge scale. This immunity is ultimately so abundant that it can finally overcome the enormous numbers of the smallpox germs which the fully developed disease presents, so that recovery ensues. But these phenomena also indicate that these enormous immune potentialities are almost never brought to bear on the germs of a smallpox infection in time to obviate material damage. It seems clear that, if these potentialities could be materialized earlier so that the germs could be quelled before they became numerous enough to produce material damage, no material damage, i.e., no "case", could develop.

Just this speeding up of specific immunity production against smallpox can be achieved by artificial postinfection immunization with vaccinia, if it be administered within a day or two after the smallpox infection.

In diphtheria immunization no analogous increase in the speed of the host's specific immunity reaction can at present be encompassed.

But two other "artificial" methods of circumventing diphtheria infection exist, both based on principles which are, in essence, those of evading any inherent delay which the host's individual speed of reaction *in re* diphtheria may entail.

In pre-antitoxin days, retrospectively considered, each nonimmune diphtheria patient who became ill depended for recovery on his own personal speed in making antitoxin. Certain infected individuals, then as now, escaped illness entirely or "had a mild case"; many, however, suffered severely and many died.

Today, however, a nonimmune individual infected with diphtheria may be at once artificially flooded with a ready-made (passive) specific antitoxic immunity. Thus the necessity of waiting, often in vain, for him to elaborate his own (active) specific immunity is obviated in time to forestall serious damage.

Also, a prospective susceptible individual, may now be treated with diphtheria toxoid well in advance of his prospective infection, to induce him to make his own antitoxin before he is infected. In this way the slow antitoxin-maker is given the relatively long time he requires to achieve a protective immunity.

In brief, the basic thesis of the speed of reaction hypothesis makes the time relationships of specific infection with specific immunity the chief controlling factor in determining the natural outcomes of infection.

Moreover, *in re* smallpox and diphtheria, as above outlined, the consonance of the hypothesis with the actual and long established facts appears to the writer as quite incontrovertible.

#### DEDUCTIONS MADE IN PREVIOUS ARTICLES

The term *infection* is herein used to mean the lodgment of an invading living pathogen in, sometimes on, e.g., diphtheria, living body tissues with subsequent successful growth and fission for at least a brief time. How briefly or how long the infection may flourish depends chiefly on how early or how late may be the mobilization of specific immunity against it.

In the following text, the living, virulent, human type tubercle bacillus is the invader chiefly discussed; the host is the North American white; both these restrictions are made for simplicity and concreteness; nevertheless, the hypothesis is held to apply, *mutatis mutandis*, to all immunity-eliciting pathogens, and to all peoples; tubercle being, so to speak, merely a "slow-motion movie" of the more acute infectious diseases.

*Size of initial dose:* The number of the living bacilli in the initial dose of a naturally acquired tubercle infection does not necessarily control the final outcome of the infection as to damage, recovery or death. But this number does affect the length of the incubation period, i.e., the length of the interval between the date of infection and the date of first recognizable material damage.

What really determines whether the final outcome of a given tubercle infection will be (a) no material damage; (b) material damage with recovery; or (c) material damage with death, is, rather, the number of bacilli which may be ultimately attained by the multiplication of the initial dose and of its descendants within the body tissues.

This ultimate number is determined, regardless of the size of the initial num-



ber, first by the degree of the suitability of the site of infection to the nutritional and other needs of the bacilli; and then by the degree of success which the body tissues may attain in frustrating the fissioning of the bacilli or in neutralizing their metabolic products, or both.

To effect such a frustration of fission for even a single living tubercle bacillus established in the tissues is to cut down the ultimate total bacillus-load of the body, not merely by this one bacillus, but also by the very numerous potential descendants which otherwise this bacillus would have had. For example, even at only its tenth fission one bacillus will yield, if not interfered with, 1,024 living bacilli, and 1,023 others which "have had their day" in between, 2,047 in all. Each of these 2,047 bacilli has produced during its own individual brief lifetime its one quota of metabolic products, 2,047 such quotas in only 10 fissions.

It is the activities of these quotas which induce from the tissues the phenomena of the infection.

*Natural checks on fission:* The body tissues follow at least two outstanding methods in attempting the frustration of the bacillary fissions: (a) a specific *biophysical-chemical interference* with the "normal" bacillary metabolism, stopping fission, probably also killing the bacillus, and perhaps also neutralizing its "toxins"; (b) a nonspecific *biophysical extrusion*—a casting forth of the bacilli, living and dead, from the body in the body discharges to the outer world in sputum, feces, urine, or through fistulae.

Such extrusions are common to all the infectious diseases and are the very cause of their infectious or communicable character.

#### SPECIFIC IMMUNITY IN TUBERCLE

The specific immunity herein considered is obviously not merely that "specific immune body" immunity which may be recognized by laboratory tests. Whatever the relationships of such immune bodies may be, it seems clear that they cannot constitute more than parts of that whole specific immunity which reveals itself in its totality through its gross effects *in vivo*.

This broader concept of specific immunity is also the oldest. It was recognized, at least in part, long before its constituent mechanisms were scientifically sought. For example, the recognition of a specific immunity to a second attack of smallpox, conferred by a first attack, long antedates any appreciation of the detail as to how it arose.

Post-morbid immunity is visualized by this hypothesis as a carry over into the recovered state of the surplus product of those immunogenic body mechanisms which had as their primary objective an intra-morbid struggle for mere survival, not a post-morbid safety. It was, as now seems clear, specific intra-morbidly induced immunity which ensured the recovery; not the recovery that ensured the post-morbid immunity (14).

For convenience, this intra-morbid immunity which results in recovery herein is termed *concurrent immunity*, as it is induced by, and exists contemporaneously with, the living infection itself. If and when this concurrent immunity has quelled the bacilli which induced it, no further immunity production can occur because the source of the immunity-eliciting stimulus has been thus destroyed.

Only the unused surplus of the concurrent immunity remains (unused and surplus just because there now remains no living infection for it to act on) and so becomes the post-morbid immunity. This surplus, leftover concurrent immunity is herein termed *free immunity*; for, having no longer any living bacilli from the now destroyed infection to act on, it presents no further active function, playing only a waiting rôle unless and until a new cognate infection occurs.

This free immunity is therefore properly regarded as protective (until it fades) against a potential danger i.e., against a further, necessarily exogenous, cognate infection.

It would appear that concurrent immunity is not protective in this same sense, for it is already fully employed in combating the actual existing infection which induced it and cannot be diverted with advantage from this combat to devote itself to intercurrent new cognate infections.

It is conceivable, of course, that, if and when such a new infection should occur in the course of an existing infection (i.e., a superinfection), the existing concurrent immunity might be diverted from combating the old infection to attacking the new. But such a transfer of the concurrent immunity activities, however successful in reducing or even destroying the new infection, would leave the old infection to flourish unrestrained (3).

As tubercle superinfections not infrequently occur in the presence of concurrent immunity, it seems unlikely that such transfer of concurrent immunity from the old infection to the new superinfection does commonly occur. For if superinfections were thus commonly destroyed, the original infection would thereby commonly lose to the superinfection at least part of its own concurrent immunity; and thus become, as the one great result of superinfections, the main locally expanding focus.

So also with metastases from the old focus. If the concurrent immunity of the old focus were diverted to follow and subdue these metastases, such metastases would be rare; and again great expansions of the original focus would be common, whereas the reverse is the more usual.

#### NONSPECIFIC EXTRUSION

Adjuvant to the specific concurrent immunity above sketched is the non-specific extrusion of living bacilli from the body. Necessarily, all living tubercle bacilli so extruded cease to contribute descendants to the bacillary load of the body, just as conclusively as they would have ceased so to do if they had been killed in the tissues by the specific concurrent immunity.

Extrusions of living bacilli from any existing focus, regardless of whether the extruded bacilli pass out of the body or move by lymph or blood stream or the bronchi, et cetera, to another part of the same body, nevertheless deplete the bacilli of that particular focus from which they come, which depletion may be great enough to result in the healing of that focus (17).

#### METASTASES

If such extruded bacilli locate successfully in a tissue site equally favorable to fission as was the focus from which they came, they will continue to fission in

this new site as they would have done in the old site had they remained there. Hence such a metastasis, while setting up a new focus, maintains but does not add to, the total bacillary load of the body.

If the extruded bacilli locate in a tissue which is less favorable to fission than the old focus, e.g., an extrusion from lung to muscle, they may perish without fission, thus paralleling a loss of bacilli extruded wholly from the tissues.

If, however, such metastases occur from a less favorable site to one more favorable, e.g., from a lung rendered physiologically subnormal by successful collapse to a more physiologically normal contralateral lung, the metastasized bacilli may fission as well in this second lung as they would have done in the first lung had the latter not been collapsed.

Losses of living bacilli by extrusion from the bodies of short time-lag individuals will ordinarily be too small (for obvious reasons) to aid materially their highly efficient (because early appearing) specific concurrent immunity.

Also, in long time-lag individuals, no great effect of such extrusions on the final fatal outcome may be expected, except to delay it somewhat; although such extrusions may reach, in the sputum alone, 10,000,000 or more tubercle bacilli per day in advanced cases (16). Even such "large" bacillary losses will usually form a quite insignificant fraction of the total bacillary load which such advanced cases are already carrying within their tissues. Moreover, this load is tending to nearly double by its own fissions alone, perhaps each day.

But in the medium time-lag individuals, the concurrent immunity by itself may be barely able to catch up with the continuously fissioning bacilli or may be a long time in so doing. Here extrusions of bacilli from the body may so reduce the total bacillary load as to doubly ensure ultimate recovery or even to materially hasten it.

#### SUPERINFECTIONS

Superinfections, i.e., cognate exogenous infections during the course of an already established infection, differ from metastases in that superinfections add to the total already existing bacillary load of the body a new reinforcement, quite independent of the endogenous increases of the original infection which are already in progress. Metastases, however, add no more to the existing bacillary load than do shifts of an existing human population from one part of a country to another add to the population of that country.

#### NEW FOCUS SITES

Both superinfections and metastases tend to set up more or less successful new foci, just as immigrants, as well as internal shifts of native populations, may set up new communities. Therefore, both superinfections and metastases tend to introduce bacilli into hitherto uninvaded areas of the body. Metastases are far more efficacious in this respect because of their relatively much greater frequency of occurrence.

Metastases constitute the normal necessary biological method by which the existing bacilli spread out from existing foci to new areas and may occur daily.

Superinfections, however, occur only as an occasional result of a sociological accident, i.e., the exposure of the host to an extraneous infective source. In these days such an accident does not necessarily occur at all or only at relatively long intervals.

Thus both metastases and superinfections may add to the total amount of body tissue which is undergoing pathological change, i.e., both tend to increase the total of material damage. But because either may invade hitherto uninvaded organs of the body, they may thus also spread damage to organs more important to the body economy than is the organ originally infected. For example, relatively small tissue damage to the meninges will entail far more damage to the body economy as a whole than much more extensive damage would entail if it were confined to less strategically important sites, such as lung or liver.

Hence the sites of metastases and of superinfections may outweigh in importance their respective initial sizes, or even their respective frequencies, in deciding their ultimate effects.

#### APPARENT PARADOXES

*Therefore it becomes possible for a medium time-lag individual, or even a short time-lag individual, to die of a tubercle infection which ordinarily he would survive, provided that the original infection, metastasis, or superinfection should locate in a strategically important structure rather than in tissues less crucially essential to survival.*

Also it may be seen that an explanation consonant with the hypothesis may be had for the complete recovery of an individual from one attack of tuberculosis, with reversion to a negative tuberculin reaction with subsequent death from a new tubercle infection without change in his genetic time-lag. The recovery from the first attack indicates that the individual concerned does not possess a short time-lag, or he would not have become materially ill; nor does he possess a long time-lag, or (therapeusis aside) he would have died. But if his necessarily intermediate time-lag was so close to the danger line that early and liberal extrusions in his first attack were requisite to tip the scales to his recovery, less liberal extrusions during his second attack, or merely their later appearance, might tip the scales the other way, with eventual death (3). Moreover, the respective sites of location of the lesions in the two attacks may be the decisive factor in the respective outcomes.

#### EARLY EXTRUSION

Just as the efficiency of specific immunity depends on the speed with which it appears, rather than on its absolute amount, so does the efficiency of extrusion from the tissues also depend on the time of its appearance in the course of the infection, rather than on how large such extrusions may be.

#### EARLY THERAPEUSIS

With an efficient bacteriostatic or bactericidal chemotherapeutic agent, the earlier in the course of an infection it begins to act, i.e., the fewer the bacilli

so far produced by the infection, the more efficient will be the chemotherapy. If administration be delayed, more intensive treatment will be needed because the bacilli have been increasing in number during the delay.

Convalescent measles serum may be also very properly considered as illustrating the same principle (3).

*Pneumothorax*: Successful pneumothorax exemplifies the same point. The earlier collapse is induced, the greater will be its effect in cutting down the bacilli. This effect is probably not exerted by increasing either specific immunity or nonspecific extrusion of bacilli.

Pneumothorax would appear to act first by checking, then by stopping, fission. This method is obviously nonspecific and acts by making the local conditions in the lung so unfavorable for the bacilli that they fail to mature sufficiently for fission. These unfavorable conditions probably consist of alterations in oxygen and carbon dioxide tensions and in reduction of the food supply and the waste disposal facilities. Before collapse, all the local nutritional lung conditions were sufficiently favorable to the entering bacilli that they could and did lodge and fission therein, producing the disease for which the collapse was initiated.

Thus it would appear that the initial flourishing of the bacilli correlates with the relative normality of the physiological conditions in the as yet uncollapsed lung; and that the disappearance of the bacilli from the collapsed lung correlates with the development of change in the physiological conditions of the latter.

It should also be noted that, even while the bacilli are disappearing from the abnormal collapsed lung, such bacilli as may enter the relatively normal contralateral lung (by metastasis or by superinfection) may flourish there, as did the bacilli of the original infection.

#### PARASITIC PATHOGENS

The basic situation seems to be that *Mycobacterium tuberculosis v. hominis* is a fairly strict parasite which requires fairly normal living tissues to which it is well adapted.

*In vivo*, the parasite enjoys, on first entering normal tissues, exactly that constant fresh supply of nutrients continuously brought to it through the very same circulatory system which the body cells require and depend on for their own well-being. In the same manner the parasitic invader shares with the body cells the similarly continuous waste disposal facilities which the same circulatory system also provides.

*In vitro*, the food is qualitatively and quantitatively different, and the speeds of food supply and of waste disposal depend rather on slow diffusion than on a rapid systemic circulation. Moreover, *in vitro*, the strongly parasitic tubercle bacillus usually receives long-dead material for food, i.e., a saprophytic diet, on which it relatively languishes.

#### THE RÔLE OF ENVIRONMENTAL FACTORS IN TUBERCLE

It would appear that, of the total North American whites infected with tubercle, the majority do not show material damage.

Here then are two mutual "control groups", distinguished by a very marked feature: a large group (of both sexes and all ages) on infection remains well; a smaller group, one-third as large (also consisting of both sexes and all ages) becomes sick. What factors govern this startling numerical difference in the ultimate outcome of tubercle infections? Can this difference be a consequence of any one or more of the extracorporeal factors often suggested which may be designated, briefly, "the strains of life"?

This notion becomes plausible enough if the minority of the total infected population who show sickness be alone investigated. Almost all such sick persons will show one or more of such "strains of life" in their pre-morbid or morbid histories. But so also will most well persons. Moreover, turning to the majority of the total infected who form the well control group, is it possible to conceive that, of 100,000 tubercle infections which occur in run-of-mine members of ordinary communities, only the 25,000 individuals who become sick have the "strains of life" impinging on them, while the 75,000 infected who remain well are wholly free of all such difficulties?

For example, are "phthisical habitus", infancy, adolescence, pregnancy, anxiety, bankruptcy, honeymoons or malnutrition common to all the 25,000 infected, yet wholly absent from the 75,000 infected; or do all the 25,000 receive large initial doses or superinfections, while all the 75,000 receive only small initial doses, and all escape superinfection?

*Malnutrition and tubercle:* Malnutrition gives rise to a great many disturbances of the body economy. Is there amongst these nutritional disturbances one or more which, like silica, may facilitate the multiplication of the tubercle bacillus or which may check the body's attempts at getting rid of the bacilli and their metabolic products? Is there any ordinary environmental agent known to check specific immunity production? Consider that most of the specific immunity produced in the world is made by living tissues which are undergoing disturbances of nutrition induced by the very disease against which those tissues are preparing the immunity. In brief, all active immunity in nature is a product of disease, not of health (15).

Some malnutrition is present in all populations, whether tuberculosis is present or not. Although malnutrition can have no action in precipitating tubercle damage on the uninfected, it is conceivable that, in the infected, nutritional disturbances prepare a more favorable soil for the bacilli in advance of or during a tubercle infection, or might lessen the specific body defences against infection. If so, when malnutrition and tubercle mortality increase markedly in a country, it should result in an increase in tubercle damage *in those infected individuals who normally would show no fatal damage* from their infections but now succumb because of the added factor of malnutrition. But do such infected hosts, i.e., those with short time-lags and intermediate time-lags, furnish the rise in tuberculosis mortality so often noted in war?

Malnutrition caused by war cannot be established as a cause of increases in tubercle cases and deaths, unless it is also shown that these added cases and deaths are contributed by infected individuals who, under normal conditions, would have suffered no material damage. In order to inculcate malnutrition

conclusively, it must be shown that malnutrition has so affected the ranks of the short and intermediate time-lag individuals as to precipitate unusual material damage and deaths.

In what way can malnutrition or other environmental factor be demonstrated to be a precipitating cause of tubercle damage otherwise than by showing that it precipitates damage and death *in those human hosts who would otherwise have overcome their infections* (12)?

#### SILICA AS SUCH A PRECIPITANT

Silicosis would appear to be such a factor. Its presence in a tuberculous individual who normally would show no material damage, i.e., who normally belongs to the majority, removes him from the majority who normally show no damage and adds him to the minority who usually suffer such damage. Hence, in a population which, on infection with tubercle alone, shows material damage in a minority and no material damage in the majority, the infected individuals of the latter group, who show silicotic invasion also, will reduce the usual majority of the no-damage group to a much lower value.

At first sight such change may seem to mean that at least one environmental factor (silica) definitely impinging on, in fact actually entering, the infected individual's tissues results, not only in killing intermediate time-lag tubercle hosts who, without the silica factor, would recover, but also in precipitating material damage and death in short time-lag persons who, without the silica factor, would show no material damage at all.

At least two questions at once arise: (1) Can the silica act by depressing the "general vitality" of the host or the local vitality of the lung, thus making greater the progress of the tubercle disease; or (2) is the effect of the silica rather to stimulate the growth and fission of the bacilli?

Regarding the first question, one striking effect on the lung of silica alone, or of silica plus tubercle, is fibrosis, i.e., the production of just that kind of tissue which is characteristic of healing tubercle, not of progressing tubercle. It has been held that pure silicosis may end in death from the mere reduction of the functioning pulmonary parenchyma by its replacement with fibrous tissue, together with emphysema of the unreplaced portions.

In silicosis plus tubercle, the latter progresses despite such extensive fibrosis, and the most striking feature is apparently abnormal rapidity of multiplication of the bacilli (6). The time-lag hypothesis therefore offers, in effect, that the silica so stimulates the bacilli as to shorten the bacillary period of growth from fission to maturity, i.e., to shorten the fission-interval from fission to fission. In what other manner than by shortening the fission interval could such increase in the rate of multiplication be attained? If this be correct, the numerical explanation becomes extremely simple and adequate: the genetic time-lags of the infecteds remain unchanged, but the fission-intervals of the bacilli become shortened; hence more fissions than normal occur within the period of the unchanged genetic time-lag.

The principles may be briefly sketched thus: assuming a normal multiplication

rate for tubercle bacilli in the tissues to require twenty-four hours from the fission of a parent bacillary cell which produces a given bacillus to the fission which ends the latter's career by dividing it into two new young bacilli, an immunity time-lag of seventy-two hours permits 3 fissions to occur before the immunity elicited by the parent bacillus begins to act (3). This immunity therefore impinges on the now 8x descendents of the initial 1x bacilli just after their third fission. The ultimate result is no material damage.

If the fission-interval of the bacilli be shortened by the silica from twenty-four hours to say eighteen hours, an unchanged genetic seventy-two-hour time-lag would still bring 1x immunity to bear at the end of the seventy-two hours, just as before; but this point will be just after the fourth fission of the bacilli, instead of just after the third fission. The fourth fission, therefore, would show 16x bacilli instead of the 8x bacilli of the third fission. The net result is thus identical with the situation which would exist if the time-lag were lengthened to ninety-six hours with a twenty-four-hour fission time.

Summarized, these considerations indicate that the action of silica on the course of a relatively short time-lag infection is to change its numerical outcome to that which produces material damage and death (3), i.e., in effect, to convert a short time-lag host into a longer time-lag host; but without in fact changing the genetic time-lag of the host's tissues at all.

This shortening of the bacillary fission-interval therefore necessarily hastens the total progress of the disease; a hastening wholly consonant with the well-known outcome of tubercle infection plus silica.

Keep in mind always that these numerical illustrations are intended to show the *kind* of numerical procedures by which the battles of infection *versus* specific immunity appear to be conducted. It is not to be understood that these actual battles in the tissues of any given host will follow precisely the figures of a given schedule.

#### SILICOSIS AND TUBERCLE IN CONTRAST WITH PNEUMOTHORAX

A review of the above discussion pictures pneumothorax as somewhat the converse of silica in so far as successful collapse of the lung reduces, even may end, bacillary fission; while silica tends strongly to increase multiplication of the bacilli, i.e., the rate of these fissions. Hence, a nonsilicotic intermediate or long time-lag host may recover, or at least live longer, because his bacilli have slowed or ceased fission as a result of a successful collapse; while a silica plus tubercle short time-lag person may die of tubercle because of the silica-stimulated increased rate of fission of his bacilli.

#### SUMMARY

A review with further elucidations and illustrations of the hypothesis is followed by a series of consonances, old and new, of the hypothesis, with observations of the broad phenomena of tubercle and other infectious diseases. Certain apparent dissonances are reconciled.



Pneumothorax and silicosis plus tubercle are correlated with the hypothesis; also parasitism and saprophytism in connection with environmental factors.

The effect of silica on tuberculosis is presented as a shortening of the fission-interval of the bacilli which results in effect, although not in reality, in an apparent, but not real, change in the genetic time-lag.

Hence, many of the phenomena of tubercle and other infections appear *as if* they occur in consonance with the particular *speed of reaction* which the tissues may show in responding, with active acquired immunity (antibacterial or antitoxic or both) to the specific immunogenic stimuli which the invading germs supply. In the writer's opinion, irreconcilable dissonances have not yet been encountered from any source.

#### SUMARIO

##### *El Tubérculo Considerado Epidemiológicamente*

Un repaso de la hipótesis de la "velocidad de la reacción," con nuevos ejemplos y dilucidaciones, va seguido de una serie de consonancias, viejas y nuevas, de la misma, con observaciones relativas a los fenómenos generales del tubérculo y otras enfermedades infecciosas, reconciliándose a la vez ciertas disonancias aparentes.

El neumotórax y el tubérculo silicótico son correlacionados con la hipótesis; y también el parasitismo y el saprofitismo en relación con los factores del ambiente.

El factor silicótico en el tubérculo presenta el efecto de la sílice sobre el acortamiento del intervalo de fisión de los bacilos, resultando *en efecto*, aunque no en realidad, en una alteración aparente, no real, del retardo genético.

Por esa razón muchas de los fenómenos de las infecciones tuberculosas y otras parece que ocurren en consonancia con la *velocidad de la reacción* mostrada por los tejidos al responder, con inmunidad adquirida activa (antibacteriana, o antitóxica, o ambas), a los específicos estímulos inmunógenos que aportan los gérmenes invasores. *No se han encontrado todavía disonancias irreconcilables de ninguna procedencia.*

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## GENERAL SUMMARY

HAVEN EMERSON<sup>3</sup>

Because of the death of the author before he had prepared a summary of the present, his third and final, contribution on his *Speed of Reaction Hypothesis*, this note was prepared at the suggestion of Doctor Pinner by a friend of the author who had conferred with him on many occasions while the three articles were in preparation and who is in entire accord with the principles, arguments and conclusions of the author.

In the years 1941-1943 the British Columbia Provincial Board of Health published, in twelve serial articles, *The Epidemiology of "Human" Bacillus Tuberculosis in the Human* by Dr. Hibbert Winslow Hill. In the AMERICAN REVIEW OF TUBERCULOSIS in May, 1944 and January, 1946, Doctor Hill presented new material on the theory of a genetic specificity of speed of reaction which appears to account for the three characteristic results of the invasion of the tissues of white North Americans by the human type of tubercle bacillus.

In summarizing the article of May, 1944, Doctor Hill notes that the evidence he presents justifies the conclusion that "It is not the size of the initial dose that matters so much as the size to which by bacillary fission the initial dose of infection may ultimately grow." "The time-lag between bacillary invasion and tissue response is the particular factor dealt with in four illustrative numerical examples which are offered as first approximations typical of clinical experience with tuberculosis in the human."

In the second article (January, 1946) further implications are dealt with and seven tables illustrate the numerical details of various processes, such as single infections, metastases, reinfections, etc., in the absence of immunity and in its presence. The illustrations given appear to support the theory presented and, until refuted, challenge acceptance. The quantitative numerical analysis of the process of creating adequate immunity units, or failure to provide enough to balance or overcome the results of bacillary fission of the tubercle bacilli in the body, is unique in the literature and is stimulating to thought.

In the present article epidemiological questions are posed and answered on the basis of the theory of the relative degree of promptness which the tissues of the infected person develop in response to the presence of the tubercle bacillus in the body.

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It would appear from the illustrations presented and numerically analysed that "Many of the phenomena of the tubercle and other infections appear *as if* they occur in consonance with the particular *speed of reaction* which the tissues may show in responding, with active acquired immunity (antibacterial, or anti-toxic or both) to the specific immunogenic stimuli which the invading germs supply."

The critical reader will be put to it to offer convincing rebuttal to the final statement of the author that "Irreconcilable dissonances have not yet been encountered from any source."

*As an exercise of rigorous mental discipline, these three articles are heartily recommended for the clinician, the immunologist and for the epidemiologist.*

## EDITORIAL

### Aluminum Therapy

The amount of research that has been conducted in the field of silicosis is, as far as industrial hazards are concerned, second only to research on lead. From the earliest studies emanating from South Africa up to the present time, interest in silicosis has never lessened. This is understandable if one bears in mind that silicosis presents, not only problems of disability and high cost to the industrialist and to the worker, but presents a unique feature in that it predisposes to tuberculosis. The annals of every hard rock mining community in the world bear ample testimony of this phenomenon.

The definition of silicosis, framed some years back by Pancoast, Gardner and their associates, included a statement of this increased susceptibility. Despite extensive investigations, however, the precise nature of the relationship between silicosis and tuberculosis has not been defined. So widespread is the silicosis hazard and so serious are the economic problems involved, that silicosis research continues and will continue, in all probability, for a long time.

On the face of it the remedy is simple; do away with silica dust in mine and factory atmosphere. But this is not so easy as it might appear. The application of dust control measures, on a large scale, is expensive and not always feasible, though in a majority of instances satisfactory methods of control can be effected. We have had standards for drinking water for a long time, but much, if not most, of our municipal drinking waters are chlorinated. We know how to prevent sewage pollution of drinking water, but practice lags behind knowledge so that it is still necessary to chlorinate. It is not surprising, therefore, that there should appear, sooner or later, a remedy for silicosis analogous to the use of chlorine in drinking water.

Time and space will not permit a recital of background events. Suffice it to say that some eleven years ago, Denny, Robson and Irwin of the Banting Institute demonstrated that finely divided aluminum would inhibit the action of silica in the lungs of experimental animals. Their work was checked and confirmed by others.

This discovery was widely publicized, as was natural, for silicosis is a hazard in many industries. On the basis of animal experimentation, the use of aluminum for dusting the air in work places and for direct inhalation by individuals was undertaken in mines and factories. This is being done in Canada and the United States, and foreign countries have sent over committees of investigators preliminary to instituting this method in their respective countries.

It is to be regretted that the Canadian group disseminated and popularized aluminum treatment before ascertaining the action of aluminum dust on the lungs of human beings. The informed consensus is that aluminum, inhaled, is harmless, but there is sufficient divergence from this opinion to leave an element of doubt.

When Banting introduced insulin into clinical practice, he had studied the action of the drug in human beings and had determined its proper dosage. When the health officer puts chlorine in the drinking water supply, he knows what it will do and he knows how to graduate dosage. No such comparable knowledge is available for aluminum as either a remedy or preventive of silicosis. It is obvious that when aluminum dust treatment is set up in a factory, the very nature of the attendant circumstances, including such items as turnover and absenteeism plus the total lack of knowledge of dosage, make impossible any scientifically controlled clinical study. All that is forthcoming is the statement of the individual treated that he feels better, or the same, or worse. His statements can be backed up by no roentgenologic evidence for, thus far, no improvements have been demonstrated by roentgenograms.

Where does this matter stand today? What is the present status of aluminum as a preventive or treatment for silicosis? We do not know. No progress report has been forthcoming from McIntyre Research of the work they have accomplished in the last eleven years.

There is some evidence to show that the silicotic treated by aluminum does not lose his susceptibility to tuberculosis. It is not enough to say that the treatment does no harm—we do not know that for sure.

At the meeting of the National Tuberculosis Association in June 1947, Dr. Berry, Assistant Professor of Medicine at the University of Colorado, read a paper on aluminum therapy in third stage silicosis (see page 557 this issue). This study was controlled and the results failed to demonstrate any value in the treatment for these far advanced cases. It did show what we have always known, that statements of improvement by patients have little value; the control group who received only fresh air did as well as the group who actually received aluminum.

It is to be hoped that further controlled studies will be forthcoming, and that the propagation of the aluminum treatment will be stayed until further information as to its effects is available. It is especially desirable that the possible beneficial effects on early stages of silicosis be thoroughly explored. The continuation of present practices will tend only to cause further confusion and, in the long run, may defeat the purposes which the Canadian group originally had in mind.

A. J. LANZA

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